INTRAMOLECULAR CYCLIZATION STRATEGIES FOR SYNTHESIZING MEDIUM-RING POLYCYCLES AND THE TOTAL SYNTHESIS OF NATURAL PRODUCTS

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INTRAMOLECULAR CYCLIZATION STRATEGIES FOR SYNTHESIZING MEDIUM-RING POLYCYCLES AND THE TOTAL SYNTHESIS OF NATURAL PRODUCTS

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To my parents and my wife Swati

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$AgBF_4$	silver tetrafluoroborate
Ar	aryl group
ATR-IR	attenuated total reflectance infrared spectroscopy
BOC	tert-butyloxycarbonyl
br	broad
°C	degrees Celsius
Cbz	carboxybenzyl
CCl_4	carbon tetrachloride
$CDCl_3$	deuterated-chloroform
CH_2Cl_2 or DCM	dichloromethane
CH_3COOH	acetic acid
Conc.	concentrated
conv.	conversion
COSY	correlated spectroscopy
CSA	camphor sulfonic acid
D-A	donor-acceptor
D-A-A	donor-acceptor-acceptor
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	1.1 2,3-dichloro-5,6-dicyano-*p*-benzoquinone
dd	doublet of doublets
δ	chemical shift

DEPT	distortionless enhancement by polarization transfer NMR spectroscopy
DHF	dihydrofuran
DMF	dimethyl formamide
DMAC	dimethylacetamide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
EDG	electron donating group
eq	equation
equiv.	equivalent
Et_2O	diethyl ether
EtOAc	ethyl acetate
EWG	electron withdrawing group
FCP	formylcyclopropane
FT-IR	Fourier-transform infrared spectroscopy
g	grams
h	hour
H_2O	water
HRMS	high resolution mass spectroscopy
IR	infrared
J	coupling constant
kcal	kilocalorie
K_2CO_3	potassium carbonate

LA	Lewis acid
LAH	lithium aluminum hydride
LDA	lithium diisopropyl amide
LiHDMS	lithium bis(trimethylsilyl)amide
λ_{max}	wavelength at maximum intensity
m	multiplet
M	molar
Me	methyl
$MeNO_2$	nitromethane
MeOH	methanol
$MgSO_4$	magnesium sulfate
mg	milligrams
MHz	megahertz
mL	milliliters
min	minutes
mmol	millimole
MMC	methyl malonyl chloride
m. p.	melting point
MS	mass spectrometry
M.S.	molecular sieves
m/z	mass to charge ratio (mass spectroscopy)
NaH	sodium hydride
$NaSO_4$	sodium sulfate

NHC	*N*-heterocyclic carbenes
NMR	nuclear magnetic resonance
NA	not applicable
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Nu	nucleophile
OTf	triflate
Pd/C	palladium on carbon
PG	protecting group
Ph	phenyl
PhMe	toluene
PhOMe	anisole
Phth	pthalimido
PMP	4-methoxyphenyl
PPA	polyphosphoric acid
ppm	parts per million
pyr.	pyridine
Quant.	quantitative
Rec.	recovered
R_f	retention factor (TLC)
$Rh_2(Oct)_4$	rhodium octanoate, dimer
Rh_2esp_2	bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)]

$Rh_2(OAc)_4$	rhodium acetate, dimer
rt	room temperature
s	singlet
satd.	saturated
SM	starting material
t	triplet
TBDMS	*tert*-butyldimethylsilane
TBDPS	*tert*-butyldiphenylsilane
tert	tertiary
TFA	trifluroacetic acid
THF	tetrahydropyran
$TiCl_4$	titanium tetrachloride
TLC	thin-layer chromatography
TMS	trimethylsilyl
$TMSN_3$	trimehtyl silyl azide
TsN_3	tosyl azide
UV-vis	ultraviolet-visible

SUMMARY

Carbo- and heterocyclic architectures occur in many bioactive natural products and synthetic drugs, and these structural units are also known to serve as important intermediates in organic synthesis. Although numerous methods exist to construct these skeletons, they often require elevated reaction temperatures and/or prolonged reaction times, stoichiometric or excess amounts of reaction promoters, and harsh reaction conditions. These limitations severely restrict their application and thus constitute a challenge in targeted syntheses. This thesis documents our recent progress in the development of novel $In(OTf)_3$-catalyzed reactions to construct useful complex carbocycles and heterocycles, as well as their applications in the synthesis of natural products and related molecular analogs.

Donor–acceptor cyclopropanes serve as synthetic building blocks for the construction of various carbo- and heterocyclic compounds due to their relative ease of ring-opening under milder conditions. Along these lines, we report the development of a new formal homo-Nazarov cyclization of alkenyl cyclopropyl ketones and heteroaryl cyclopropyl ketones, catalyzed by $In(OTf)_3$. The reactions provided functionalized cyclohexenones/cyclohexenols and heteroaromatic ring-fused cyclohexanones in good to excellent yields. The studies showed that electron-rich, electron-neutral, and electron-poor aromatics, heteroatoms, silylmethyl groups on the cyclopropyl are well tolerated.

As an extension of the scope and applicability of donor-acceptor cyclopropyl based cyclizations, we explored the $In(OTf)_3$-catalyzed tandem cyclopropane ring-opening/Friedel-Crafts alkylation reaction of methyl 1-(1*H*-indolecarbonyl)-1-

cyclopropanecarboxylates. The reaction found to be tolerant of electron-rich, electron-neutral, and electron-poor aromatics, heteroaromatics, heteroatoms, and silylmethyl groups on the cyclopropanes. The protocol affords functionalized hydropyrido[1,2-*a*]indole-6(7*H*)-ones in up to 99% yield from readily-available indoles and alkenes. This skeleton appears in the core structures of an impressive number of naturally-occurring indole alkaloids and pharmaceutically relevant compounds.

The functionalized pyrrolo[1,2-*a*]indoles and pyrrolo[3,2-1-*ij*]quinolines are unique structural features present in a wide range of heterocyclic compounds that play an important role in medicinal chemistry and organic synthesis. A simple and efficient approach to the synthesis of these useful skeletons is to utilize *N*-indolyl alkylidene malonate monoamides as cyclization precursors. An In(III)-catalyzed intramolecular Friedel-Crafts alkylation reaction of substituted methyl 2-(1*H*-indole-1-carbonyl)acrylates was developed. The reaction occurs under mild conditions, affording the corresponding products in good to excellent yields (up to 98%) with high diastereoselectivities (up to >99:1 *dr*).

Finally, the versatility of our cyclization method is demonstrated by its successful application in the diastereoselective synthesis of (±)-deethyleburnamonine. The key steps of the synthesis involve: (a) a tandem ring-opening/Friedel-Crafts alkylation to assemble the tetracyclic ABDE ring system with a *cis* D/E fused ring junction; (b) a TFA-promoted *N*-Boc deprotection/*N*-alkylation to generate the C-ring; and (3) a Krapcho decarbalkoxylation to generate the target. Using this protocol, (±)-deethyleburnamonine was accomplished in 18% overall yield over six steps.

CHAPTER 1

INDIUM(III)-TRIFLATE CATALYSIS IN ORGANIC SYNTHESIS

1.1. INTRODUCTION

In 1861, German scientist Ferdinand Reich and Hieronymus Theoder Richter were the first to discover Indium, which was isolated from heating zinc ores in the flame of a Bunsen burner.[1] This accidently discovered metal was named *indium* for the brilliant unique indigo lines seen in its atomic spectrum. Since then, indium has been primarily used in alloys for the electronics industry and as a medical diagnostic agent. Although it belongs to the same group as boron and aluminum which has a number of applications since their discoveries, indium remained largely unexplored in organic synthesis.[2] One hundred and fourteen years later, Rieke and co-worker's disclosure of an indium-mediated Reformatsky-type reaction of ethyl bromoacetate with carbonyl compounds initiated a strong interest among synthetic chemists.[3] In 1988, Butsugan *et.al* reported the allylation of carbonyl compounds using organoindium species under mild conditions.[4] However, indium metal emerged as a one of high potential in organic synthesis when Chan and coworkers reported an *In*-mediated allylation of aldehydes and ketones in aqueous media and demonstrated the use of organoindiums to achieve a Grignard-type reaction in the presence of water.[5] Since then, the intriguing properties of this metal have led to an enormous development in indium catalysis chemistry, as evidenced by the large number of monographs, accounts, and reviews.[6]

The intriguing property of indium that makes it unique in its application as reagent/catalyst is its first ionization potential (FIP). When compared to the elements of group 13 and the metal elements near it the periodic table, indium has the lowest first ionization potential. Surprisingly, the ionization potential of indium is not only much lower than that of boron, aluminum, tin, zinc, magnesium, copper, thallium, gallium but also as low as most active alkali metals such as sodium and lithium (Table 1.1).[7]

Table 1.1. First Ionization Potentials (FIP) of Some Elements

Metal	In	B	Al	Ga	Tl	Sn	Zn	Mg	Cu	Na	Li
FIP (eV)	5.78	8.29	5.98	5.99	6.10	7.34	9.39	7.64	7.72	5.13	5.39

When oxidation potentials (E^o) of two most common oxidation states of indium (In^+ and In^{3+}) are compared against other metal elements, the oxidation potential of In^+ and In^{3+} were found to be relatively low (Table 1.2).[8] These values become important as they directly relate to the reactions taking place in the solutions. Despite low FIP and E^o values, indium metal is inert to boiling water or alkali and does not oxidize readily upon exposure to air. This is contrary to reactive alkali metals (Na, Li, and K). The organoindium compounds are known to be less reactive than alkyllithiums and Grignard reagents.[9] These characteristic features makes metal indium-catalyzed reactions more interesting to explore as they offer more control with respect to selectivity, reactivity, and air-sensitivity.[10]

Table 1.2. Oxidation Potentials (E^o) of Some Elements

Element	In^+	In^{3+}	Cr	Al	Ga	Tl	Zn	Mg	Na	Li	K
$\mathbf{E^o}$ **(*V*)**	0.14	0.44	0.74	1.66	0.54	0.74	0.76	2.37	2.71	3.04	2.93

1.2.CARBO- AND HETEROCYCLIC COMPOUND SYNTHESIS

Carbo- and heterocyclic compounds occur in many bioactive natural products and synthetic drugs, and these structural units are also known to serve as important intermediates in organic synthesis. Numerous methods described in the literature utilize the unparalleled reactivity of organoindium species and In(III)-salts in Lewis acid-promoted reactions to generate diversified carbo- and heterocyclic skeletons. The intention is to highlight some of the recent work rather than present an exhaustive review. More specifically, $In(OTf)_3$ catalyzed reactions are covered in this dissertation. Therefore, it is recommended to the reader that the reviews of previous researchers be read for additional information.

1.2.1. HYDROTHIOLATION OF ALKYNES

In(III)-catalyzed substrate-selective hydrothiolation of terminal alkynes was developed recently by Prajapati and co-workers.[11] When 2-mercaptobenzothiazole **I-1** was reacted with phenylacetylene **I-2**, Markovnikov's hydrothiolation product **I-3** was isolated in 90% yield (Figure 1.1). Prajapati also screened a wide variety of heteroaromatics, thiols and alkynes, and a smooth reaction was observed in all cases, providing product in excellent yields. However, when cyclohexyl thiol **I-4** was reacted

with phenylacetylene **I-2** under identical reaction conditions, it furnished the anti-Markovnikov hydrothiolation product **I-5** in 85% yield. Various aliphatic and aromatic thiols under similar conditions afforded a mixture of *E/Z*-vinyl sulfides in excellent yield, however it was determined that these conditions were substrate-dependent. As anticipated, the thermodynamically stable *E*-isomer was predominantly favored over *Z*-isomer in almost all the cases.

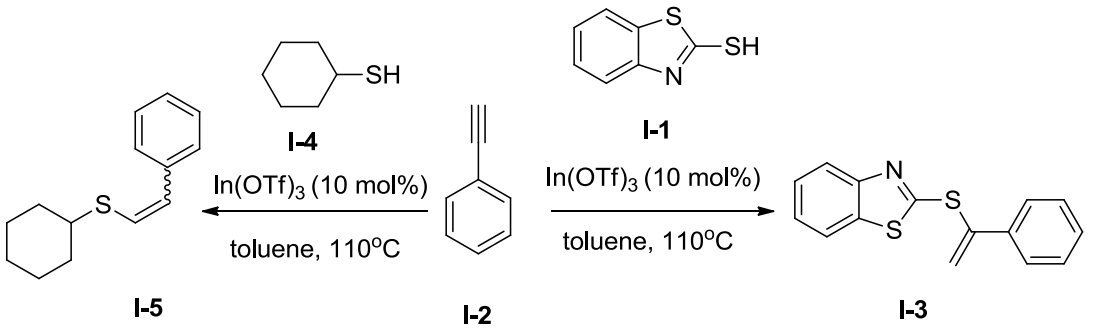

Figure 1.1. Indium(III)-Catalyzed Hydrothiolation of Alkynes

1.2.2. MULTI-COMPONENT REACTION

The isocyanide based Passerini three component reaction has been well studied due to its ability to synthesize compounds with structural diversity.[12] This reaction generates α-acyloxyamides from the reaction of aldehydes, isocyanides, and carboxylic acids.[13] In 2009, Taguchi *et al.* developed a Passerini three component reaction that forms α–alkoxyamides in good yields from the $In(OTf)_3$-catalyzed reaction of aldehydes, isocyanides, and free aliphatic alcohols.[14] In continuation of their efforts, Taguchi reported four component reactions of aldehydes **I-6**, isocyanides **I-7**, and trimethylsilyl azide **I-8** in alcoholic solvents to give highly substituted 1*H*-tetrazoles **I-9** in good yields (Figure 1.2).

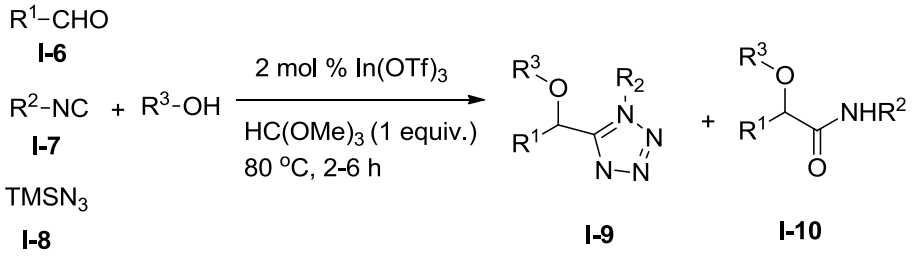

Figure 1.2. Indium(III)-Catalyzed Multi-Component Reaction

1.2.3. CARBON NUCLEOPHILIC ADDITION REACTION

Recently, Matsuo and co-workers reported an In(III)-catalyzed addition of carbon nucleophile to nitrones.[15] While attempting to generate a seven-membered ring compounds **I-14** by the nucleophilic addition of cyclobutanone **I-11** to nitrones **I-12** followed by the ring cleavage of four-membered ring intermediate species, Matuso observed the unexpected formation of a γ-butyrolactone derivatives **I-13** (Figure 1.3). Further investigation to expand the scope of the reaction various nitrones were employed to generate products in moderate to good yields and with very high diastereoselectivities.

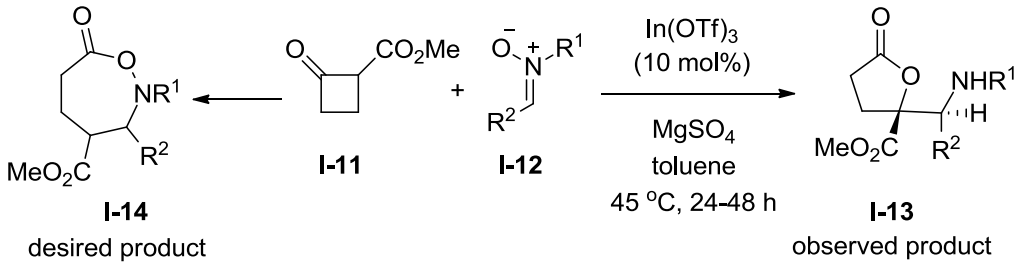

Figure 1.3. Indium(III)-Catalyzed Carbon Nucleophilic Addition Reaction

1.2.4. INTRAMOLECULAR PRINS CYCLIZATION

The intermolecular Prins cyclization has emerged as a powerful synthetic strategy to generate highly functionalized tetrahydropyran scaffolds,[16] whereas its intramolecular version is very useful in the stereoselective synthesis of angularly fused oxa-bicycles and tricycles.[17] In continuation of their research on the Prins cyclization, the Yadav group recently reported the stereoselective synthesis of *trans*- and *cis*-fused hexahydro-2*H*-furo[3,2-*c*]pyran and octahydropyrano[4,3-*b*]pyran scaffolds.[18] When benzyl ether **I-15** was reacted with DDQ in the presence of $In(OTf)_3$ it furnished products **I-16** and **I-17** in good yields and excellent stereoselectivity (Figure 1.4). This is reaction is proposed to proceed through oxidative cyclization with DDQ followed by a sequential C-H bond activation and an intramolecular Prins cyclization.

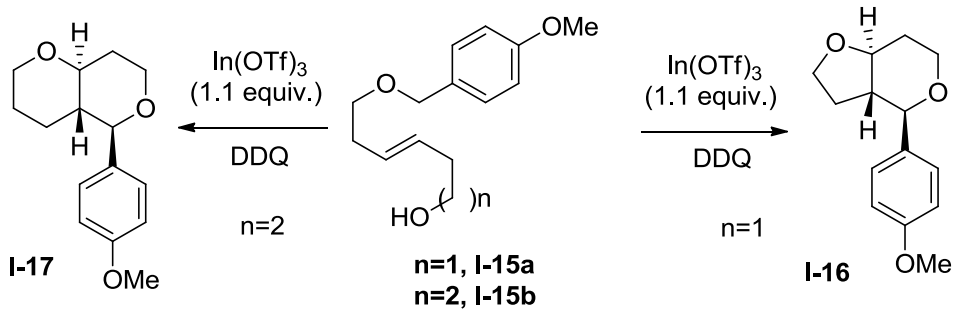

Figure 1.4. Indium(III)-Catalyzed Intramolecular Prins Cyclization Reaction

1.2.5. OXONIUM-ENE REACTION

Oxonium-ene reactions are important in organic synthesis due to their ability to construct a wide variety of functionalized cyclic ethers namely, tetrahydropyrans, tetrahydrofurans, and oxabicyclic compounds that are known to exhibit interesting

biological activities.[19] The Saikia group recently reported the stereoselective synthesis of oxabicyclo[3.2.1]octene via a (3,5)-oxonium-ene-type reaction.[20] Under $In(OTf)_3$ catalysis, oxabicycle **I-21 or I-22** was generated by the reaction of (-)-terpinen-4-ol **I-20** with aldehydes **I-18** or epoxides **I-19,** respectively (Figure 1.5).

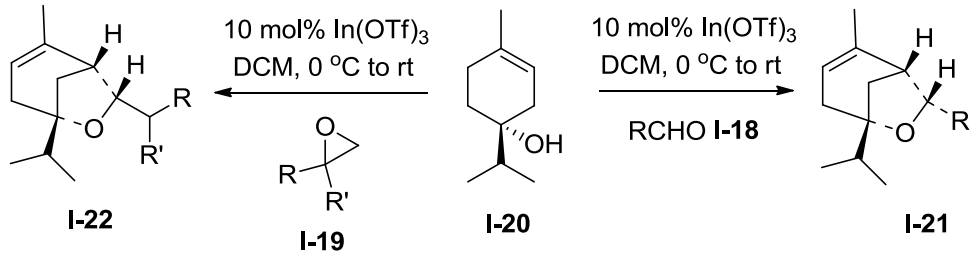

Figure 1.5. Indium(III)-Catalyzed Oxonium-Ene Reaction

1.2.6. ALLYLIC C-H OXIDATION

Allylic C-H oxidation of olefins provides a very powerful synthetic tool to introduce wide variety of functionality into molecules.[21] Recently, Shi used $In(OTf)_3$ to successfully promote allylic C-H oxidation of aryl cycloalkanes **I-23** with *N*-propylthiosuccinimide **II-24** in the presence of various nucleophiles to provide allylic ethers, esters, and sulfonamides **I-25** in 49-83% yields (Figure 1.6).[22] Shi proposed that the reaction proceeds through the formation of a thiiranium species to generate an allyl sulfide intermediate which then reacts with the requisite nucleophiles to form the desired allylic products **I-25**.

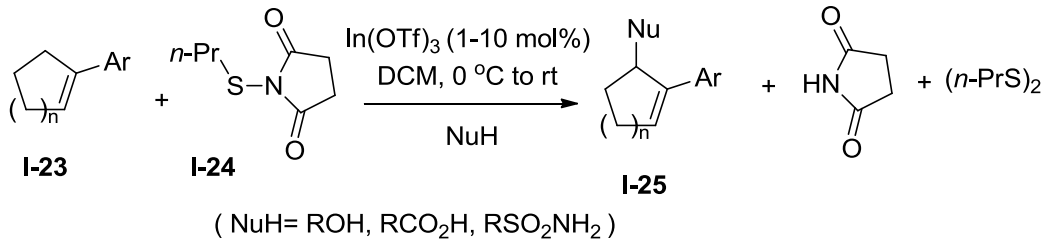

Figure 1.6. C-H Oxidation via Indium(III)-Catalysis

1.2.7. FRIEDEL-CRAFTS/CONJUGATE ADDITION REACTION

Friedel-Crafts alkylation is the most commonly used method for synthesis of elaborate heteroaromatic compounds.[23] Along these lines, Trost and co-workers reported the tandem ruthenium/indium catalysis of propargylic alcohols.[24] When propargylic alcohols **I-26** were exposed to the mixture of ruthenium complex, indium triflate, and *R*-camphorsulfonic acid (CSA), followed by addition to heteroarenes **I-27**, provided an atom-economical access to β-heteroarylated ketones **I-28** (Figure 1.7). The reaction is proposed to go through a Ru-catalyzed redox isomerization of propargylic alcohols to enones (electrophile), followed by $In(OTf)_3$ catalyzed Friedel-Crafts/conjugate addition reaction. Trost demonstrated that both electron-rich and neutral heteroarenes undergo this tandem reaction sequences smoothly to generate products in yields up to 97%.

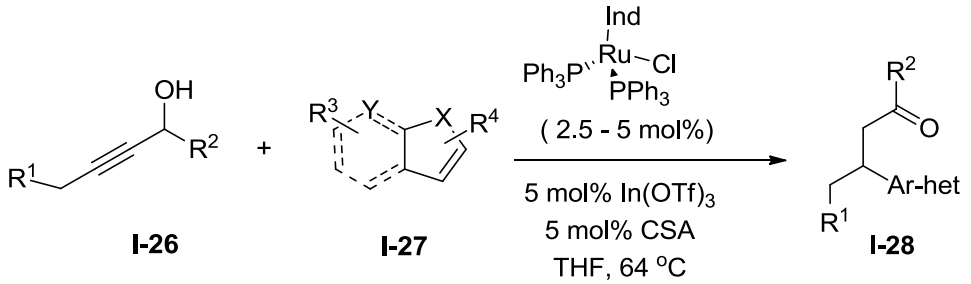

Figure 1.7. Ru/In-Cocatalyzed Redox Isomerization/F-C/Conjugate Addition Reaction

1.2.8. CONIA-ENE REACTION

A large number of metal-catalyzed Conia-ene reactions have been described for the preparation of heterocycles such as 3-methylene pyrrolidines and tetrahydrofurans.[25] In 2008, Hatakeyama reported an indium-promoted Conia-ene-type reaction of nitrogen- and oxygen-tethered acetylenic malonic esters **I-29** to form pyrrolidinones and other heterocyclic products **I-30** (Figure 1.8).[26] Further in their studies, Hatakeyama elegantly illustrated the power of this methodology towards the synthesis of (-)-salinosporamide A **I-31,** a highly potent 20S proteasome inhibitor.

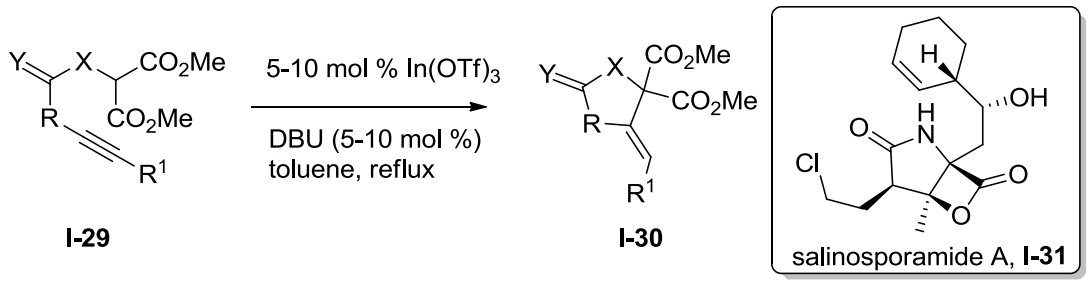

Figure 1.8. Indium (III)-Catalyzed Conia-Ene Reaction

1.2.9. [2+2] CYCLOADDITION

The [2+2] cycloaddition presents a straightforward and efficient method for the synthesis of cyclobutane and their derivatives.[27] Cyclobutane fragments are a key motif found in a large number of biologically important natural products.[28] The Loh group reported an indium(III)-catalyzed highly efficient intramolecular [2+2] cycloaddition reaction between the distal allenic double bond and unactivated alkene moieties of **I-32**.[29] The reaction is proposed to go through a [$_{\pi}2_{s}$+$_{\pi}2_{a}$] concerted mechanism involving a vinylic cation species. Further investigation demonstrated that the reaction is highly

chemo- and regioselective and also tolerates a variety of ene-allenones **I-32** to furnish the strained bicyclo[n.2.0] skeletones **I-33** in high yields and with excellent diastereoselectivities (Figure 1.9).

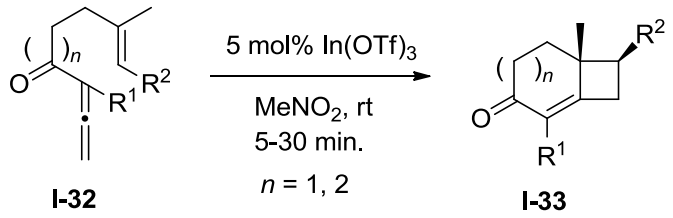

Figure 1.9. [2+2] Intramolecular Cycloaddition of Ene-Allenones via In(III)-Catalysis

1.2.10. HETERO DIELS-ALDER REACTION

The hetero Diels-Alder reaction is one of the most powerful tools used in generating highly substituted dihydropyranones, a key structural element present in many bioactive products and important pharmaceuticals.[30] Feng and co-workers reported $In(OTf)_3$ catalyzed hetero Diels-Alder reactions.[31] The reaction of aldehydes **I-35** with diene **I-34** in the presence of 5 mol% of an aromatic amide derived *N*,*N*'-dioxide/$In(OTf)_3$ (1:1) complex in anisole formed hetero Diels-Alder products **I-36** (Figure 1.10). The Feng group also demonstrated the utility of this reaction through their gram-scale synthesis of a triketide. In a continuation of asymmetric indium-catalyzed hetero Diels-Alder work, the Feng group recently reported an efficient synthesis of β-methoxy-γ-methyl α,β-unsaturated δ-lactones **I-39**.[32] The hetero Diels-Alder reaction of the Brassard-type dienes **I-37** and aldehydes **I-38** furnished δ-lactones **I-39** in good yields as well as *dr* and *ee* values.

Additionally, Feng showed that these products can be easily transformed into the methyl-protected *epi*-prelactones upon hydrogenation.

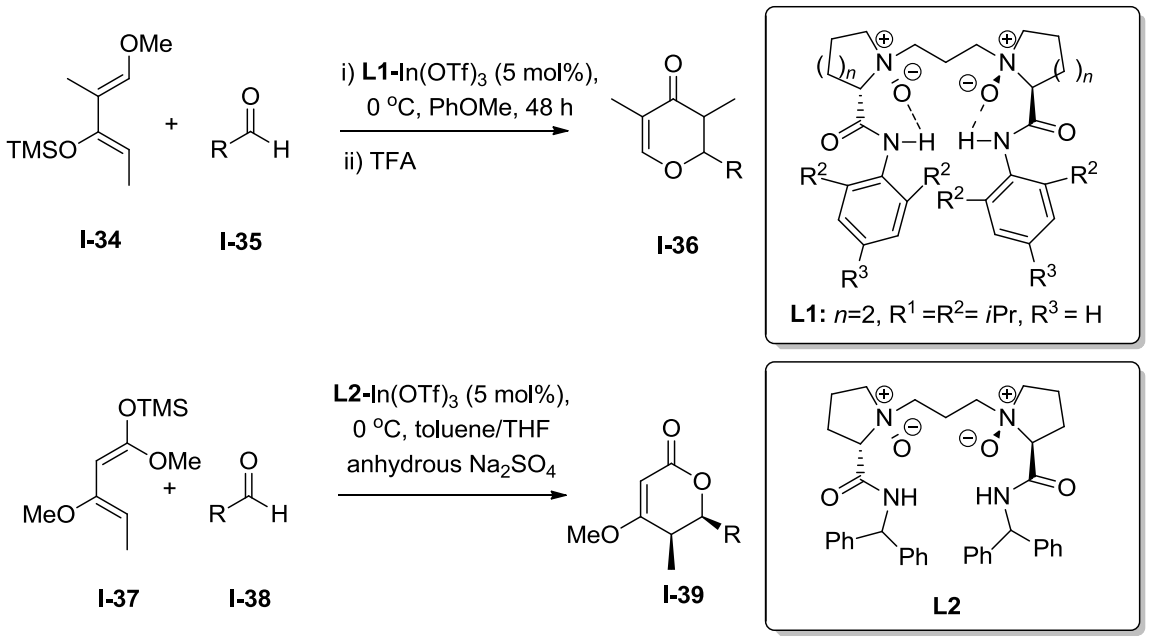

Figure 1.10. Hetero Diels-Alder Reactions Between Dienes and Aldehydes

1.2.11. NUCLEOPHILIC AROMATIC SUBSTITUTIONS

Heteroaromatic compounds bearing heteroaryl-heteroaryl bonds are a privileged class of building blocks found in a wide variety of areas such as liquid crystals, optoelectronic materials, biological molecules, and ligands for asymmetric catalysis. Even though nucleophilic aromatic substitutions (S_NAr) reactions have been known since the 1940, the majority of these compounds have recently been synthesized using a transition metal-catalyzed cross-coupling reaction.[33] Within this context, the Tsuchimoto group reported indium-catalyzed heteroaryl-heteroaryl bond formation through nucleophilic aromatic substitution in 2011.[34] Starting from 2- or 3-methoxythiophenes **I-41**, the addition of 1.3 equiv. of substituted indoles **I-40** in the presence of indium triflate

underwent a S_NAr reaction to afford heteroaryl products **I-42** (Figure 1.11). The author also showed that quarter-heteroaryl compounds can easily be synthesized using this strategy.

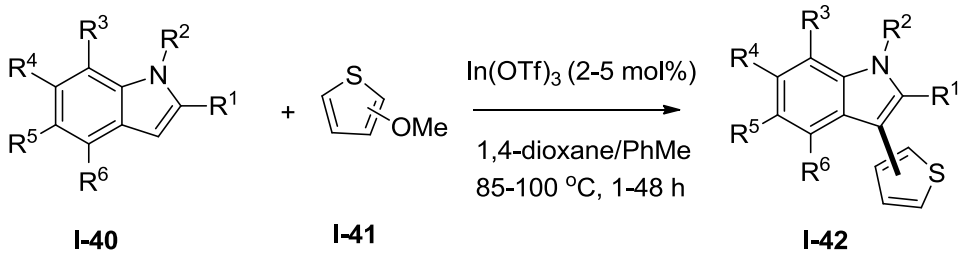

Figure 1.11. In(III)-Catalyzed Aromatic Nucleophilic Substitution Reaction

1.2.12. ALLYLATION

Allylation of aldehydes is one of the most commonly used strategies to generate homoallylic alcohols, which are versatile building blocks in organic synthesis.[35] Allylsilanes and allylstannanes have been used as potential reagents for allylation reactions due to their fascinating and excellent reactivity.[36] Along these lines, Yoda and co-workers developed an efficient synthetic method for chiral α-methylene-γ-lactones **I-46**.[37] An In-catalyzed enantioselective allylation takes place when aldehydes **I-44** was reacted with β-carbonyl allylstannanes **I-43**. The resulting products, upon subjecting to acidic hydrolysis, afforded γ-lactones in high yields (Figure 1.12).

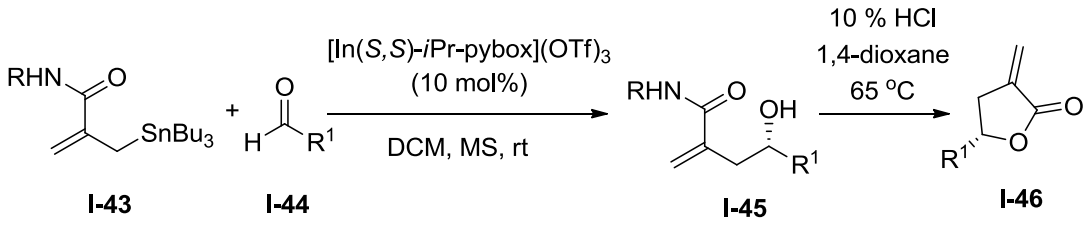

Figure 1.12. In(III)-Catalyzed Enantioselective Allylation of Aldehydes

1.2.13. C-S CROSS-COUPLING REACTIONS

Aryl sulfides are a key motif found in numerous pharmaceutically active compounds as well as in a large number of drugs in therapeutic areas, such as immune, inflammatory, diabetes, Parkinson's and Alzheimer's diseases. In 2008, Rao and co-workers developed indium-catalyzed C-S cross-coupling reaction.[38] When aryl halides **I-47** were treated with alkane thiols **I-48** in the presence of $In(OTf)_3$, the reactions proceeded smoothly to afford the corresponding aryl sulfides **I-49** in good to excellent yields (Figure 1.13).

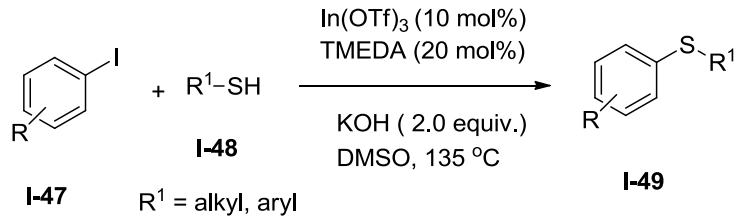

Figure 1.13. C-S Cross-Coupling Reaction of Aryl Halides with Alkane Thiols

1.3. SCOPE OF WORK

Over the last two decades, indium triflate has emerged as a promising catalyst for various types of organic reactions involving carbon-carbon bond formation and other organic transformations to construct carbo- and heterocyclic molecules. Indium catalysis is of great interest to synthetic organic chemist primarily due to its stability in air and water, reactivities, selectivities, low toxicity, recyclability, and milder reaction conditions. Due to the unique advantages of indium over other commonly used metals, the France group decided to explore further utility of indium catalysis in organic synthesis.

Chapter 2 in this thesis is focused on developing an In(III)-catalyzed efficient protocol for the formal homo-Nazarov cyclizations of alkenyl cyclopropyl ketones and heteroaryl cyclopropyl ketones. In this reaction, vinyl cyclopropyl ketones (or heteroaryl) cyclopropyl ketones are converted into cyclohexenones and heteroaryl ring-fused cyclohexanone derivatives.[39] These viable approaches remained relatively underexplored. Previous approaches suffer from one or many of the following drawbacks: (a) narrow substrate scope; (b) longer reaction times; (c) poor yields; and (d) harsh reaction conditions- a large excess of acid and high temperatures.[40] One reasonable approach to circumvent all these drawbacks is to utilize donor-acceptor cyclopropyl vinyl ketones **I-50** bearing a secondary electron acceptor group (such as an ester) in the α-position. The France group strongly believed that the secondary acceptor group would facilitate coordination with Lewis acids, thereby allowing milder reaction conditions for cyclopropane ring-opening **A**. An ester acceptor group would also serve to further polarize the resulting cyclic oxyallyl cation **B** by localizing the charge density (Figure 1.14).

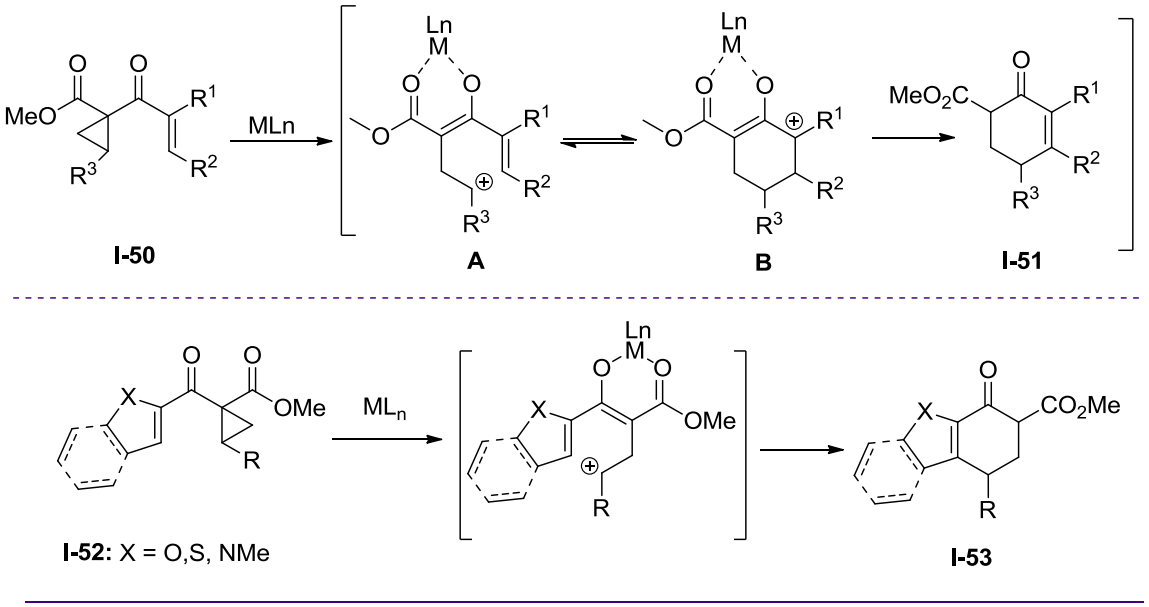

Figure 1.14. Proposed Formal homo-Nazarov Cyclization Reaction

The hydropyrido[1,2-*a*]indole skeleton and, more specifically, its C(6)-oxidized cogeners, are key structural motifs that appear in the core structures of an impressive number of naturally-occurring indole alkaloids and pharmaceutically relevant compounds.[41] Despite several reported approaches to construct hydropyrido[1,2-*a*]indole-based polycyclic skeletons, an efficient synthesis still remains a formidable goal for organic chemists.[42] Chapter 3 in this thesis reports the synthesis of densely functionalized hydropyrido[1,2-*a*]indole-6(7*H*)-ones derivatives **I-55** via $In(OTf)_3$-catalyzed tandem cyclopropane ring-opening/Friedel–Crafts alkylation sequence of methyl 1-(1*H*-indolecarbonyl)-1-cyclopropane carboxylates **I-54**, thereby potentially providing a method that is highly modular, operationally simple and amenable to a large variety of functional groups and substitution patterns (Figure 1.15).

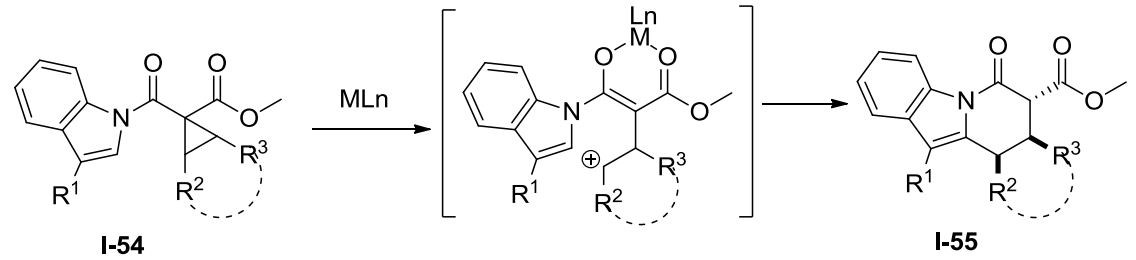

Figure 1.15. Proposed Tandem Cyclopropane Ring-Opening/Friedel-Crafts Alkylation

[*a*]-Annelated indoles such as the pyrrolo[1,2-*a*]-indoles are unique structural features present in a wide range of heterocyclic compounds that play important roles in medicinal chemistry and organic synthesis.[43] Numerous routes to the pyrrolo[1,2-*a*]indoles have been reported in recent years. However, these methods do not allow for a variety of functionality to be incorporated about the 1*H*-pyrrolo[1,2-*a*]indole skeleton.[44] In chapter 4, we report an $In(OTf)_3$-mediated diastereoselective intramolecular Friedel-Crafts cyclizations of substituted methyl 2-(1*H*-indole-1-carbonyl)acrylates **I-56** to generate functionalized 1*H*-pyrrolo[1,2-*a*]indole derivatives **I-57** (Figure 1.16).

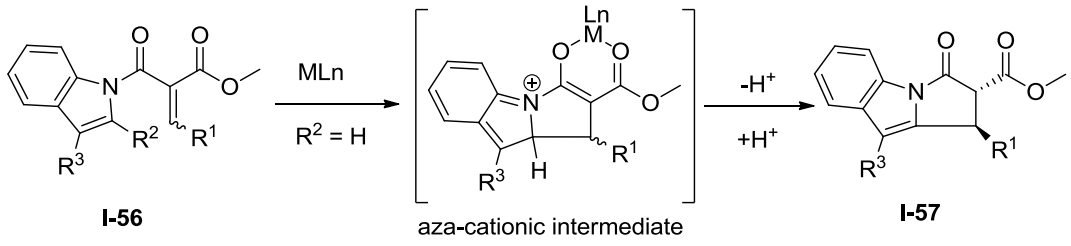

Figure 1.16. Proposed Intramolecular Friedel-Crafts Cyclization Reaction

The tetrahydroquinoline (THQ) moiety is one of the most privileged class of nitrogen-containing compounds, being widespread in nature and found as a key structural unit in a large number of therapeutic agents.[45] Within the THQ class of compounds, the

4*H*-pyrrolo[3,2,1-*ij*]quinolines, as well as their reduced and oxidized derivatives have garnered considerable attention in the area of drug discovery and agrochemistry.[46] Chapter 5 includes our efforts to develop an effective strategy to access 4*H*-pyrrolo[3,2,1-*ij*]quinoline derivatives **I-59** using $In(OTf)_3$-catalyzed diastereoselective intramolecular Friedel-Crafts cyclizations reaction of substituted methyl 2-(2-methyl-1*H*-indole-carbonyl)acrylates **I-58** (Figure 1.17).

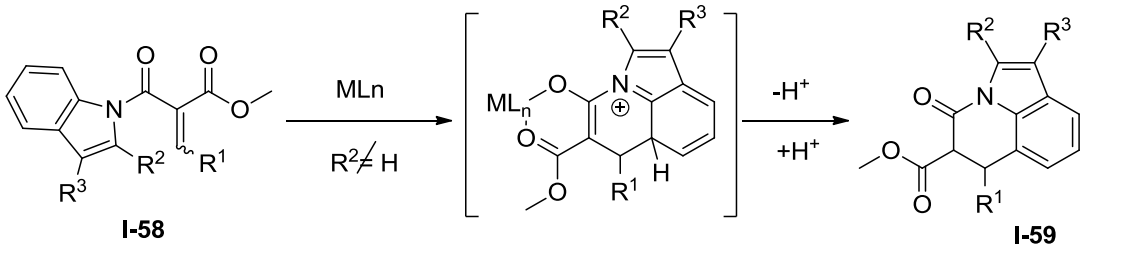

Figure 1.17. Proposed Protocol to Access 4*H*-Pyrrolo[3,2,1-*ij*]quinoline derivatives

Chapter 6 discusses our efforts in the synthesis of (±)-deethyleburnamonine, using our catalytic tandem ring-opening/Friedel-Crafts alkylation protocol. (±)-Deethyleburnamonine is chosen because it represents the simplest example of both the *eburnan-vinca* and *tacaman* alkaloids, with interesting pharmacological activities.[47] In comparison to the previously described synthetic routes to this natural product, our highly modular, operationally simple In(III)-catalyzed protocol allows for a large variety of functional group and substitution modifications in the molecular architecture.

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CHAPTER 2

INDIUM(III)-CATALYZED FORMAL HOMO-NAZAROV CYCLIZATIONS OF ALKENYL CYCLOPROPYL KETONES AND HETEROARYL CYCLOPROPYL KETONES*

2.1. INTRODUCTION AND BACKGROUND OF CYCLOPROPANES

The smallest cycloalkane, the cyclopropane was first synthesized by W. H. Perkin[1] through the attack of a diethyl malonate dianion upon 1,2-dibromoethane in 1984. Since then organic chemists have always been intrigued by the cyclopropane subunit.[2,3] Cylopropanes are the basic core of a wide range of natural products and compounds with interesting biological activities.[4] Furthermore, several cyclopropane-containing unnatural products have been tested for their bonding features[2d,5] and enzyme mechanism/inhibition.[6] Additionally, these highly strained cycloalkanes have been used as versatile intermediates in the synthesis of several functionalized cycloalkanes and acyclic compounds.[2c,7] The following section will provide a brief overview of the theoretical basis for the unusual reactivity and properties of cyclopropanes.

* This work was performed in collaboration with Lien H. Phun and Marchello A. Cavitt, fellow graduate

2.1.1 BONDING IN CYCLOPROPANES

Among cycloalkanes, the cyclopropane and its derivatives represent a unique class of compounds by virtue of their unusual structural, spectroscopic, and chemical properties.[5a] In its simplest graphical representation, the cyclopropane can be viewed as a planar equilateral triangle with internal angles being 60^{o}. However, these bond angles are considerably less than the ideal value of 109.5^{o} for sp^3-hybridized orbitals. This deviation imparts considerable angular (Bayer) strain. Additionally, cyclopropanes suffer from torsional (Pitzer) strain due to the rigid, coplanar arrangement of the three carbon atoms, thereby causing eclipsing of ring substituents (Figure 2.1). The release of the ring strain (27.5 kcal/mol) associated with ring-opening provides the rationalization for high reactivity and the thermodynamic driving force for these reactions.[8]

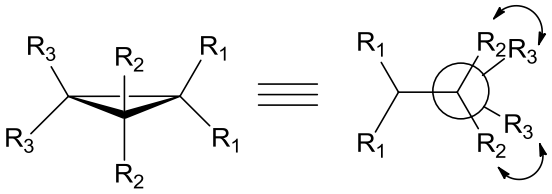


Figure 2.1. Torsional (Pitzer) Strain in Cyclopropanes

The cyclopropanes have higher percentage of *s* character of the C-C bond forming orbitals, shortened interatomic bond distances, and weaker C-C bonds. They also have the ability to interact with neighboring π-electron systems and *p*-electron centers, form metal complexes, add reagents (strong acids, halogens, ozone), and undergo catalytic hydrogenation and cycloaddition reactions. To accommodate all of these, two alternative models have been presented: the Coulson-Moffit[9] and Walsh models[10] (Figure 2.2).

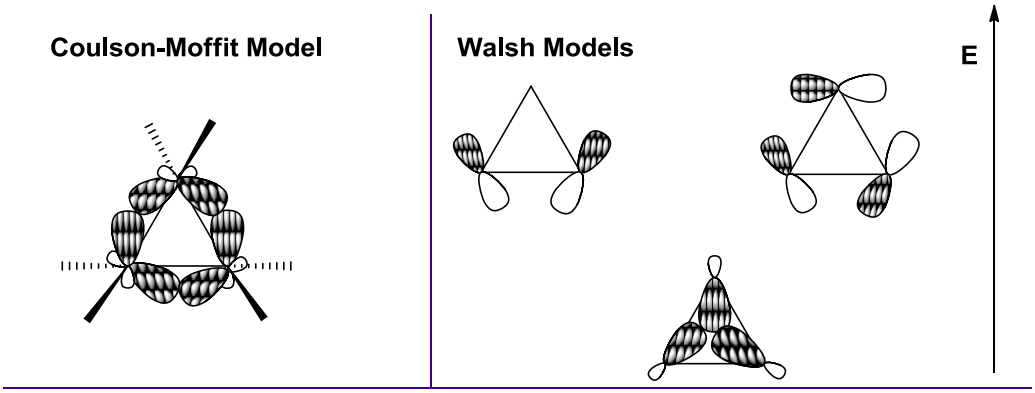


Figure 2.2. The Coulson-Moffit and Walsh Model for Cyclopropane Bonding

Unactivated cyclopropanes have been directly employed for certain useful chemical transformations.[11] However, the ring-opening reactions of monoactivated cyclopropanes are in general sluggish due to their low reactivities. Therefore, severe conditions are required. For example, cyclopropanes are either treated with strong nucleophiles (such as I^-),[12] stronger Lewis acids (such as $TiCl_4$),[13] or assisted by the β-stabilizing effect of the silicon atom of trimethylsilyl group.[14] To facilitate ring-opening under mild reaction conditions, these strained cycloalkanes require further activation from electron-donating or accepting substituents. The facile cyclopropane ring-opening towards nucleophiles or electrophiles is often dictated by the electronics of the substituents on the ring[2c]. For example, cyclopropanes substituted with electron-donating groups are activated for C-C bond cleavage in the presence of electrophiles affording the cation equivalent for further reactions (Figure 2.3, Eq.1). Whereas, cyclopropane substituted with electron-accepting groups behave more like homo-Michael acceptors in the nucleophile initiated ring-opening to generate an anion equivalent for further chemical transformations (Figure 2.3, Eq.2).

The reactivity of cyclopropanes is further enhanced by substituting it with both donor and acceptor (D-A) groups, guaranteeing activation of the cyclopropanes and a high versatility of the products after ring-opening.[15] This is achieved by placing D-A groups on the cyclopropane either geminally or vicinally. The use of geminal D-A substituted cyclopropanes in organic synthesis has been restricted due to the competing electronic effects of the two substituents that offer litter to no bond polarization. On the contrary, vicinal D-A cyclopropanes have been extensively studied over the past two decades.[2a,2c,16] Such an arrangement of substituents with opposite electronic effects imparts reactivity to the cyclopropanes by a synergistic electron "push-pull" relationship. These results in an improved ability of vicinal D-A substituents on the cyclopropanes to stabilize the dipolar intermediate species formed upon heterolytic C-C α-bond cleavage. For this reason, under Lewis acidic conditions, vicinal D-A cyclopropanes undergo formal retro-aldol rearrangement to form 1,3-zwitterionic intermediates species that could served as 1,3-dipolar synthons in several valuable chemical transformations (Figure 2.3, Eq.3).

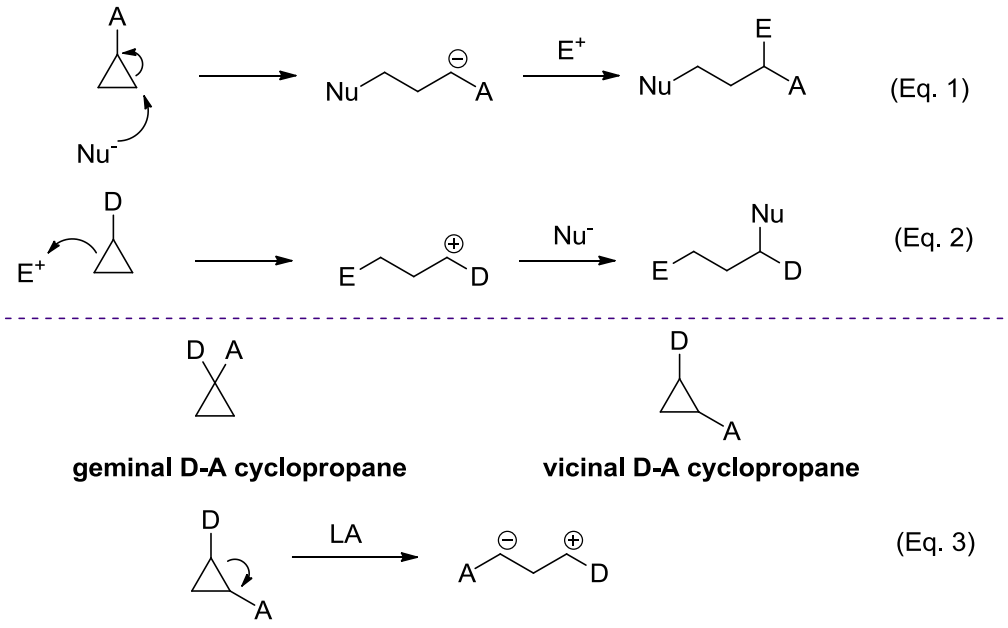


Figure 2.3. Effect of Donor-Acceptor Substituents on the Cyclopropane Reactivity

2.2. VICINAL DONOR-ACCEPTOR CYCLOPROPANES IN ORGANIC SYNTHESIS

The pioneering work of Cram and Danishefsky on vicinal D-A cyclopropanes provided better insight into the mechanistic understanding of the ring-opening reactions of D-A cyclopropanes.[16a,17] Owing to the relative ease of ring-opening under a variety of mild Lewis-acid conditions, vicinal D-A cyclopropanes gained considerable attention as powerful synthetic building blocks towards the construction of highly functionalized carbo- and heterocyclic compounds. The chemistry of vicinal D-A cyclopropane is so extensive that a full discussion of all ring-opening and cyclization reactions is beyond the scope of this thesis. Therefore, only a short selection of relatively new methods for the synthesis of carbo- and heterocycles will be presented, with a focus on cycloadditions, cyclodimerizations, and formal homo-Nazarov chemistry.

2.2.1. CYCLOADDITIONS/ANNULATIONS OF CYCLOPROPANES

2.2.1.1. [3+2] CYCLOADDITION

In 2003, Kerr and co-workers reported the first homo [3+2] dipolar cycloaddition reaction of nitrones **II-1** with cyclopropane diesters **II-2** to generate tetrahydro-1,2-oxazines **II-3**.[18] In this seminal publication, Kerr elegantly utilized the reactivity of 1,1-cyclopropanediesters as one-carbon homologues of electron-deficient olefins. Ytterbium(III) triflate was identified as an effective Lewis acid promoter for this reaction. The Kerr group was also able to screen a wide variety of nitrones and 1,1-cyclopropanediesters. In every case examined, only the *cis* product was observed with yields ranging from 50-96%. The reaction is proposed to proceed through a step-wise mechanism, involving nucleophile-initiated cyclopropane ring-opening followed by a Mannich-type ring closure. Further in their studies, the utility of the reaction was demonstrated through the preparation of tricyclic precursor **II-4** for antitumor antibiotic compound FR-900482 (Figure 2.4).

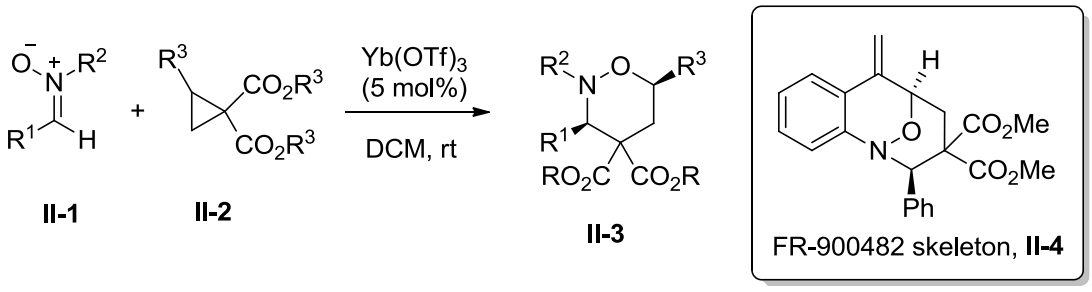


Figure 2.4. Synthesis of Tetrahydro-1,2-oxazines via Homo [3+2] Dipolar Cycloaddition of Nitrones and 1,1-Cyclopropanediesters

2.2.1.2. [3+3] CYCLOADDITION

Charette and co-workers developed a $Ni(ClO_4)_2$–mediated [3+3] cycloaddition reaction of aromatic azomethine imines **II-5** with 1,1-cyclopropanediesters **II-6** in 2008 (Figure 2.5).[19] The reaction afforded unique tricyclic pyridazino[1,6-*a*]quinolines based compounds **II-7** in moderate to high yields and modest diastereoselectivities. The higher yields were obtained when electron rich aromatic substituted cyclopropanes were employed in the reaction. However, electron poor aromatics, vinyl, and unsubstituted cyclopropanes gave significantly lower yields. Further stereochemical studies showed that the reaction proceeded in a step-wise fashion which involves nucleophilic ring-opening of cyclopropane followed by a diastereoselective ring closure reaction.

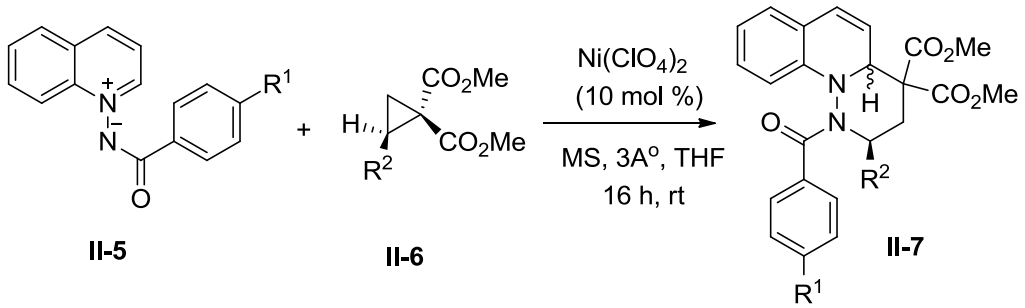


Figure 2.5. [3+3] Cycloaddition of Aromatic Azomethine and 1,1-Cyclopropanediesters

2.2.1.3. [3+4] CYCLOADDITION

In 2008, the Ivanova group developed an analogue of the Diels-Alder reaction with a cyclopropane as the dienophile. This formal [3+4] cycloaddition between isobenzofuran **II-8** with cyclopropanes **II-09** proceeds in the presence of $Yb(OTf)_3$ to yield two isomeric cycloadducts **II-10** in a combined yield of 84-92% (Figure 2.6).

The reaction is proposed to proceed through a concerted mechanism, providing the less stable *exo* isomer as the major product. This argument was confirmed when dimethyl methylenemalonate was formed as a decomposition product upon subjecting the major product to prolonged heating in the presence of catalyst. Ivanova observed a similar reaction when anthracene **II-11** and aryl substituted cyclopropanes **II-9** were reacted in the presence of $TiCl_4$, furnishing cycloadducts **II-12** in high yields.

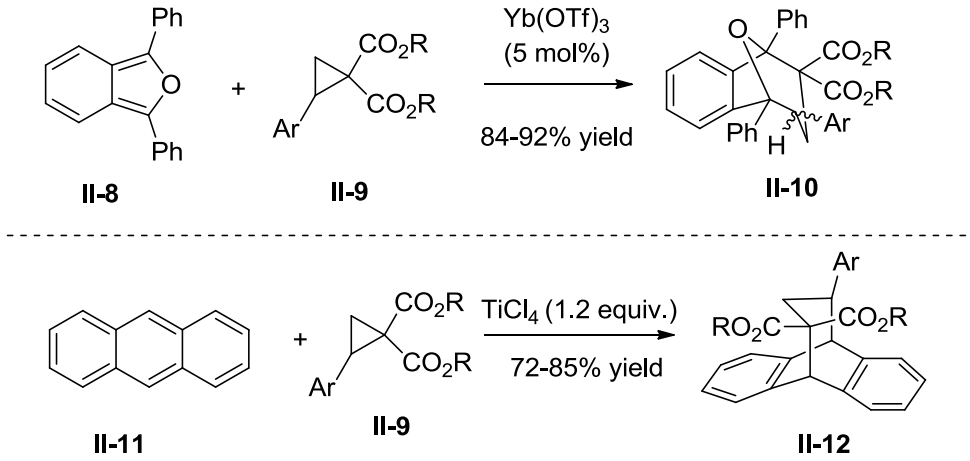


Figure 2.6. [3+4] Cycloaddition Reaction with 1,1-Cyclopropanediesters

2.2.1.4. [4+1] CYCLOADDITION

Investigations by Zhang and co-workers into the reactivity of 2-substituted or 2,3-disubstituted 1-(1-alkynyl)-cyclopropyl ketones **II-13** revealed that carbon monoxide could act as a dipolarophile in a [4+1] cycloaddition reaction with D-A cyclopropanes to afford 1,3,5-tri- and 1,3,5,6-tetrasubstituted 5,6-dihydrocyclopenta[*c*]furan-4-ones **II-14** (Figure 2.7).[20] In the presence of 5 mol% of Rh(I) catalyst, regio- and stereospecific carbonylation of 1-(1-alkynyl)cyclopropyl ketones occurred.

Alkyl, electron-donating group (EDG) and electron-withdrawing group (EWG) substituted aryl, alkene, cyclopropyl, esters, and ketone groups are well tolerated in this highly modular, atom-economical reaction with cycloaddition yields varying from 38 % to 95%. The reaction is proposed to proceed through regioselective oxidative addition of Rh(I) across C1-C2 bonds of the cyclopropane forming a rhodacyclobutane which immediately isomerizes to a furano-fused rhodacyclopentane. Finally, insertion of carbon monoxide generates the furan-fused rhodacyclohexanone derivative, which on subsequent reductive elimination furnishes the carbonylation products.

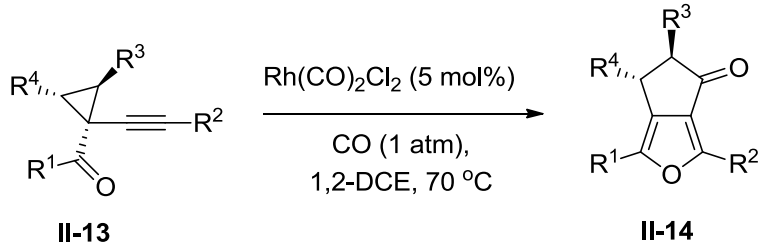


Figure 2.7. [4+1] Cycloaddition Reaction of D-A Cyclopropane with Carbon Monoxide

2.2.1.5. [4+2] CYCLOADDITION

The [4+2] cycloaddition chemistry developed by Zhang *et al.* for the synthesis carbo- and heterocycles elegantly utilizes the reaction of Au-containing all-carbon 1,4-dipoles generated from 1-(1-alkynylcyclopropyl) ketones **II-15** (Figure 2.8).[21] The reaction of D-A cyclopropane **II-15** with indoles under $IPrAuNTf_2$ promotion affords tetracyclic furan **II-16** in good to high yields, however in low diastereoselectivities. Various substituents including cyclopropyl, cyclohexyl, phenyl, and alkyl ether groups were tolerated at the alkyne terminus and at the carbonyl group.

However, a sterically demanding cyclohexyl group at the alkyne terminus lowered the yield. Further studies by Zhang showed that aldehydes/ketones can also work as a dipolarophile to furnish fused furans **II-17** high yields.

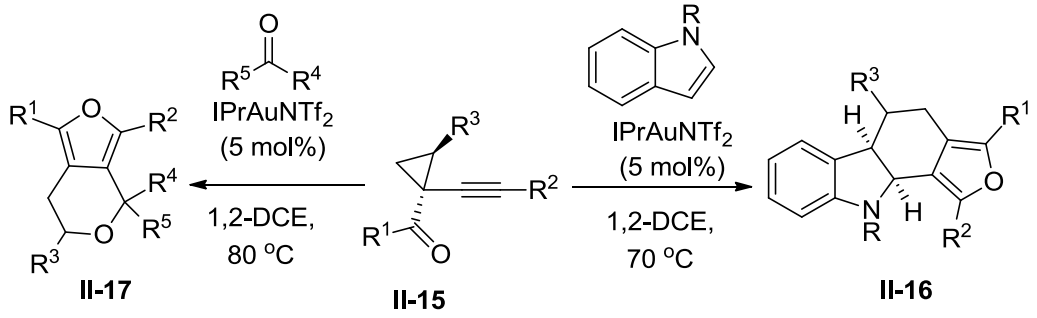


Figure 2.8. [4+2] Cycloaddition of D-A Cyclopropane with Indoles/Aldehydes/Ketones

2.2.1.6. [4+3] CYCLOADDITION

The synthesis of 5,7-fused heterobicyclic furo[3,4-d]-[1,2]oxazepines **II-18** from the [4+3] cycloaddition of D-A cyclopropyl ketones **II-17** and nitrones was described by Zhang in 2010 (Figure 2.9).[22] The regioselectivity of the reaction was achieved by making subtle changes in the choice of Lewis acid. When 1-(1-alkynyl)cyclopropyl ketone **II-17** was reacted with nitrones in the presence of 10 mol% $Sc(OTf)_3$, the reaction afforded tetrahydro-1,2-oxazines **II-19** through 1,3-dipolar (formal [3+3]) cycloaddition reaction, whereas upon reacting in the presence of 2 mol % $Ph_3PAuOTf$ it fashioned 5,7-fused products **II-18**. The reaction is effective with EDG- and EWG- substituted aryl, styryl, heteroaryl, and benzyl groups on the nitrones, and aryl, alkyl, biaryl, and cycloalkanes on the cyclopropanes furnishing products in good to excellent yields and moderate to high diastereoselectivities. The regioselectively-tunable cycloaddition was possible due to the difference in reactivity of the Lewis acids. The scandium catalyst primarily coordinated the carbonyl group whereas gold coordinated to the alkyne.

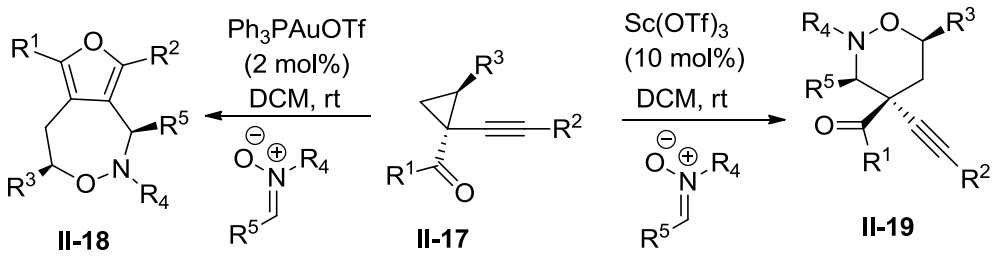


Figure 2.9. Lewis Acid Catalyzed Regioselectively Tunable Cycloaddition

2.2.2. CYCLODIMERIZATION OF CYCLOPROPANES

2.2.2.1. [3+2] CYCLODIMERIZATION

Recently, the Melnikov group reported a novel Lewis acid-catalyzed [3+2] cyclodimerization of cyclopropanes **II-13**.[23] The cyclopropanes, upon subjecting to harsh reaction conditions involving $Yb(OTf)_3$ or $Sn(OTf)_2$ in refluxing chlorobenzene, afforded highly functionalized cyclopentanes **II-14** (Figure 2.10). The proposed mechanism includes a Lewis acid catalyzed cyclopropane ring-opening with the formation of synthon **I** *(umpolung)* and its transformation into synthon **II** (normal reactivity), which provides only two-carbon units for the newly formed cyclopentane ring. The reaction worked well with aromatic, heteroaromatic, and diaryl-substituted cyclopropanes, providing products in high yields.

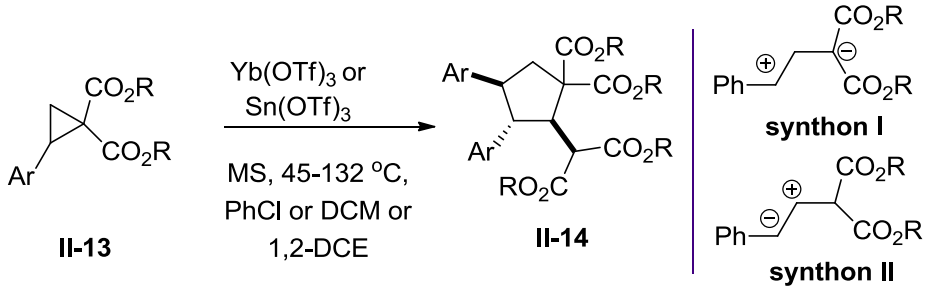


Figure 2.10. [3+2] Cyclodimerization of 1,1-Cyclopropanediesters

2.2.2.2. [3+3] CYCLODIMERIZATION

In 2011, the Ivanova group demonstrated [3+3] cyclodimerization of 1,1-cyclopropanediesters.[24] Interestingly, this reaction process provides straight-forward one-step access to three different types of six-membered cyclic compounds such as *cis*-1,4-diarylcyclohexanes **II-16**, 1-aryl-1,2,3,4-tetrahydronaphthalenes **II-17** or 9,10-dihydroanthracenes **II-18** (Figure 2.11). The product outcome was completely dependent on the reaction conditions and substituent pattern in the parent cyclopropane. The cyclodimerization leading to 1,4-diarylcyclohexanes proceeded with excellent diastereoselectivity furnishing the *cis*-isomer exclusively, while the reaction leading to 1-aryl-1,2,3,4-tetrahydronaphthalenes and 9,10-dihydroanthracenes proceeded with moderate to high diastereoselectivity with the *trans* isomer as the major product.

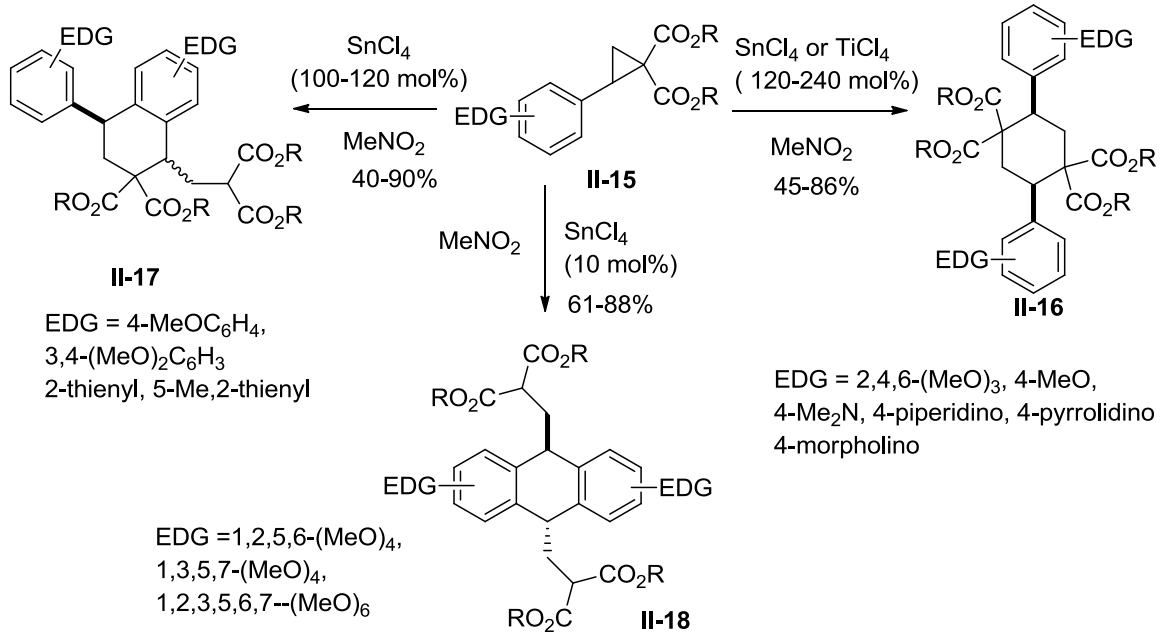


Figure 2.11. [3+3] Cyclodimerization of 1,1-Cyclopropanediesters

The D-A cyclopropanes were also known to undergo a different set of reactions when the nucleophile is intramolecularly located in the form of either an electron-rich double bond or aromatic group. One such reaction is referred to as the formal homo-Nazarov cyclization reaction. In the next section, a brief survey of the history and current state of the formal homo-Nazarov cyclization will be outlined.

2.3. FORMAL HOMO-NAZAROV CYCLIZATION REACTION

2.3.1. BACKGROUND AND INTRODUCTION

The abundance of useful compounds bearing functionalized cyclopentyl rings has led to the development of diverse methods for the construction of five-membered carbocycles. Among these methods, the Nazarov cyclization has gained prominence as a one of the most powerful methods for the construction of unsaturated five-membered rings due to the stereoselectivity and controllable regioselectivity of the reaction.[25] It is a 4π-electron process involving the conversion of divinyl ketones **II-19** to cyclopentenones by activation with protic or Lewis acids (Figure 2.12). The individual mechanistic steps involved in the Nazarov cyclization are thought to proceed as follows: i) a divinyl ketone **II-19** complexes to the acid to form a pentadienyl cation **A**; ii) a conrotatory ring closure of **A** gives an oxyallyl cation intermediate **B** with an *anti* relationship between R^1 and R^2; iii**)** removal of proton from B (eliminative pathway) or trapping of the cation in the presence of a suitable nucleophile (interrupted pathway). Both pathways terminate the reaction, leading to cyclopentenones **II-20** or dense functionalized cylopentanone **II-21**, respectively.

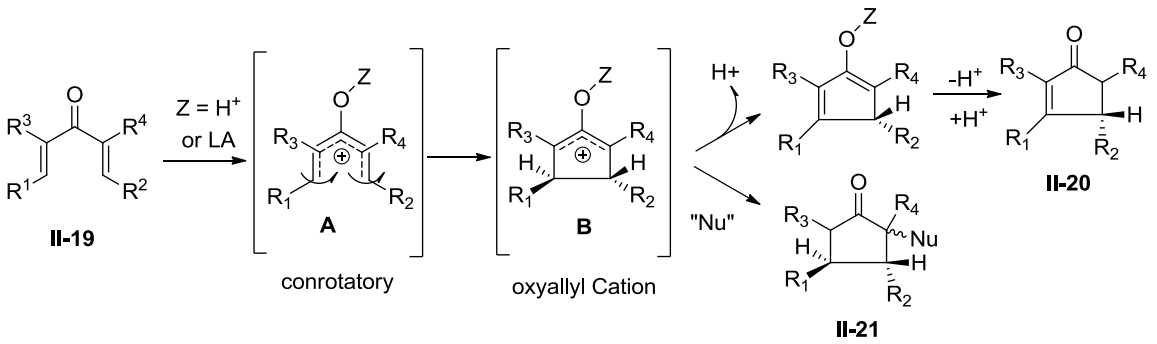


Figure 2.12. Classical Nazarov Cyclization Reaction of Divinyl Ketones

The Nazarov cyclization has gained recent attention in the literature due to several advances that have improved the synthetic utility of this transformation: (1) reactive substrates undergo cyclization using catalytic Lewis acids;[26] (2) trapping of the intermediate cation was found to be efficient, allowing preservation of both stereocenters created during conrotatory electrocyclization;[27] (3) chiral auxiliaries allow asymmetric cyclization;[28] (4) axial to tetrahedral chirality transfer is possible;[29] and (5) chiral Lewis acids afford enantioselectivity.[30] The reaction has been featured as the key step of several syntheses of natural products and other bioactive molecules, further demonstrating the utility of the cyclization for application to complex molecule synthesis.[31]

While the traditional Nazarov reaction (using divinyl ketones) has been very well-studied, much less is known about the formal homo-Nazarov cyclization, a homologous variation. In contrast to the concerted Nazarov reaction, this reaction proceeds in a stepwise fashion. In this reaction, one double bond from divinyl ketones system is masked as a cyclopropyl group. Thus, the reaction of such cyclopropyl vinyl ketones **II-22** provides an access to larger ring systems, α,β-unsaturated cyclohexenones **II-23** via a similar cyclic oxyallyl carbocation **A'** (Figure 2.13).

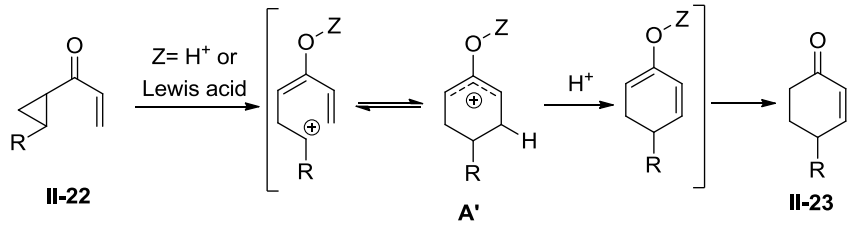


Figure 2.13. Formal Homo-Nazarov Cyclization of Cyclopropyl Vinyl Ketones

2.3.2. PREVIOUS METHODS OF ALKENYL FORMAL HOMO-NAZAROV CYCLIZATION

The first example of a formal homo-Nazarov cyclization was reported by Murphy and Wattanasin in 1980.[32] Murphy reported the synthesis of tetralones **II-25** from activated aryl aroylcyclopropanes **II-24** using a large excess of $SnCl_4$. Studies showed cleavage of only the *b* bond, since product **II-25b** was not observed. Formation of carbocationic intermediates **Int-a,** and **Int-b** has been proposed (Figure 2.14). The products yields were obtained in the range of 14-80%. When the R^2 group was incapable of stabilizing the benzyl cation **Int-a**, the reaction was slow and thus further supports the proposed cationic mechanism. Tetralone derivatives **II-25a** were obtained only when both ring substituents were suitably activated. This observation was bolstered when successful cyclization was observed only when the cyclopropane was substituted with an electron-rich aromatic group.

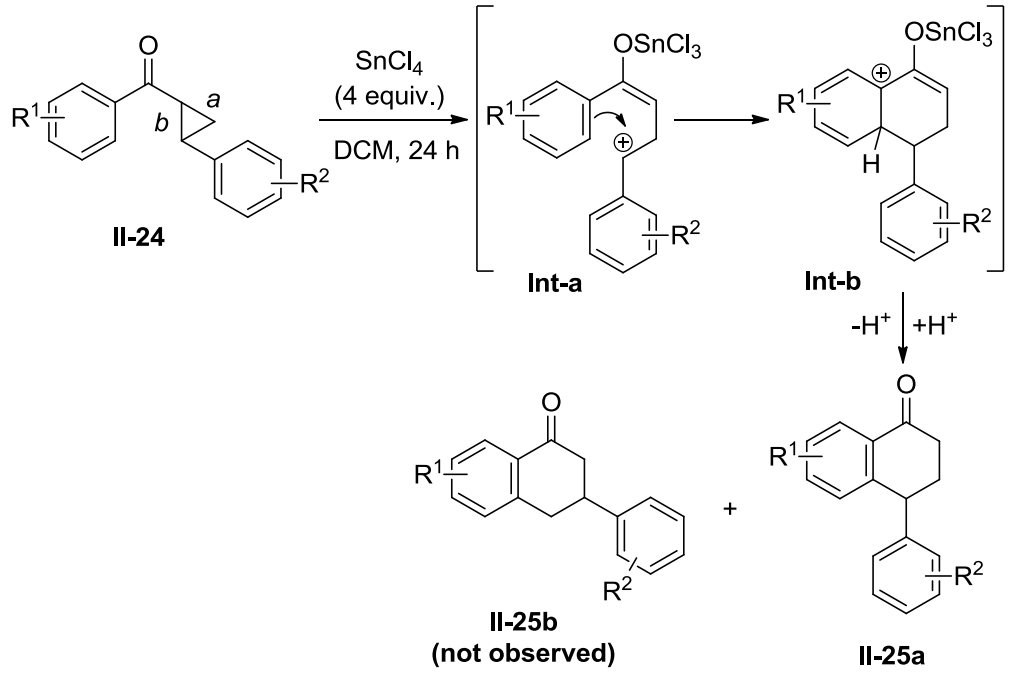


Figure 2.14. Murphy's Formal Homo-Nazarov Cyclization

Tsuge and coworkers reported the first example of formal homo-Nazarov cyclization of alkenyl cyclopropyl ketones in 1888.[33] In this seminal report, Tsuge reported the cyclization of several vinyl-cyclopropyl ketones in the presence of a large excess of polyphosphoric acid to generate cyclohexenones. In one representative example, cyclization of ketone **II-26** proceeded successfully to provide cyclohexenones product **II-27** in 63% yield (Figure 2.15). However, the reaction had three major drawbacks: (1) lack of generality - only five out of sixteen substrates provided the desired cyclohexenones; (2) poor product yields (15-63%); and (3) harsh reaction conditions -excess PPA in refluxing benzene for >24 h. All of these limitations resulted in sparse application of the alkenyl formal homo-Nazarov protocol.

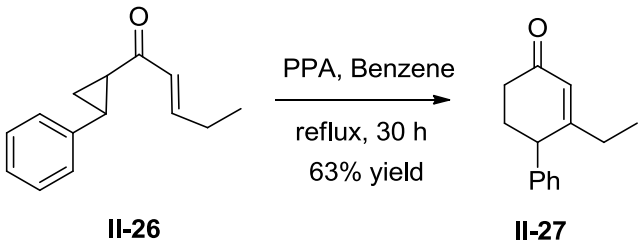


Figure 2.15. Tsuge's Formal Homo-Nazarov Cyclization

In 2009, the Waser group greatly expanded the scope of formal homo-Nazarov cyclization of alkenyl cyclopropyl ketones by utilizing cross-polarized substrates **II-28**.[34] Frontier and co-workers have demonstrated the benefit of cross-polarized substrates in the related classical Nazarov cyclization reaction.[35] Various hetero-atom activated vinyl cyclopropyl ketones **II-28** cyclized successfully to provide carbo- and heterocyclic products **II-29** in high yields under catalytic amount of TsOH (Figure 2.16). The substitution of a heteroatom α- to the ketones by a silyl group was also tolerated. When unactivated vinyl ketone **II-30** (cyclohexyl based) was subjected to the reaction conditions, none of the desired product formation was observed. The substrate either polymerized **II-31** or gave alcohol **II-32** product in 32% yield. This study has provided invaluable insight into the potential of the alkenyl reaction with two major limitations: i) simple alkenes did not work (an α-heteroatom was required to activate the alkenyl group); and ii) the necessity of having an electron-rich aromatic substituent on the cyclopropanes to promote the cyclization.

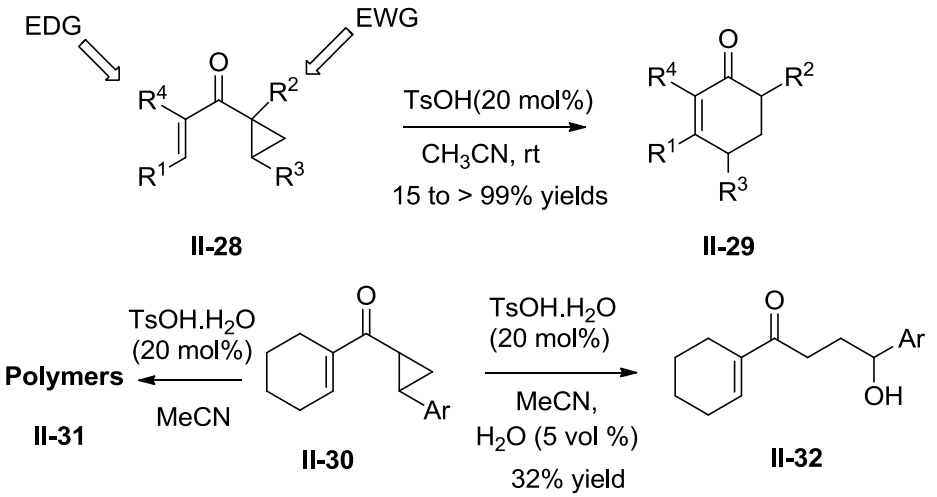


Figure 2.16. Waser's Catalytic Formal Homo-Nazarov Cyclization Approach

The examples of heteroaromatic formal homo-Nazarov cyclization reaction involving the use of heteroaromatic rings as reactive π-system, to generate heteroaryl fused-cyclohexanones ring skeletons will be discussed separately in this chapter under the section of formal homo-Nazarov cyclization of heteroaryl cyclopropyl ketones.

2.4. INDIUM(III)-CATALYZED FORMAL HOMO-NAZAROV CYCLIZATION OF ALKENYL CYCLOPROPYL KETONES[†]

As described in the previous section, only two reports on the cyclization of alkenyl (vinyl)-cyclopropyl ketones were mentioned in the literature. These methodologies suffer from one or more of these limitations: i) harsh reaction conditions-use of a large excess of acid or heating at high temperatures; ii) lower product yields; iii) lack of generality; iv) use of a heteroatom in the α-position on the vinyl group; and v) requires electron rich aryl group on the cyclopropane to promote cyclization. Unfortunately, these restrictions severely limit the scope and utility of the reaction in organic synthesis. Therefore, the development of an efficient and highly versatile protocol for the formal homo-Nazarov cyclization that can circumvent all these issues would be highly beneficial to the synthetic community.

2.4.1. REACTION DESIGN

To facilitate the formal homo-Nazarov cyclization of alkenyl cyclopropyl ketones and ultimately expand the scope and applicability of the reaction, the France lab envisioned that the introduction of a secondary electron-acceptor (an ester) in the α-position of the cyclopropane **II-33** would guarantee the activation of the cyclopropanes and circumvent the necessary reaction barrier by strongly coordinating with Lewis acids. Cyclopropanes bearing one donor and two geminal acceptors group (D-A-A) are known to undergo a rapid ring-opening due to increased polarization and elongation of the C-C bond (*a*-bond) between them. We also postulated that it would allow milder reaction

[†] This work was performed in collaboration with Lien H. Phun, a fellow graduate student in the France research group.

conditions for cyclopropane ring-opening. Substituting EWG- and EDG- groups strategically on the cyclopropane would serve to further polarize the resulting cyclic oxyallyl cation **Int-d** by localizing the charge density, which could favor the desired cyclization to furnish cyclohexenones **II-34** (Figure 2.17). Frontier has similarly demonstrated the benefit of using esters as acceptor groups to polarize the classic Nazarov cyclization.[35]

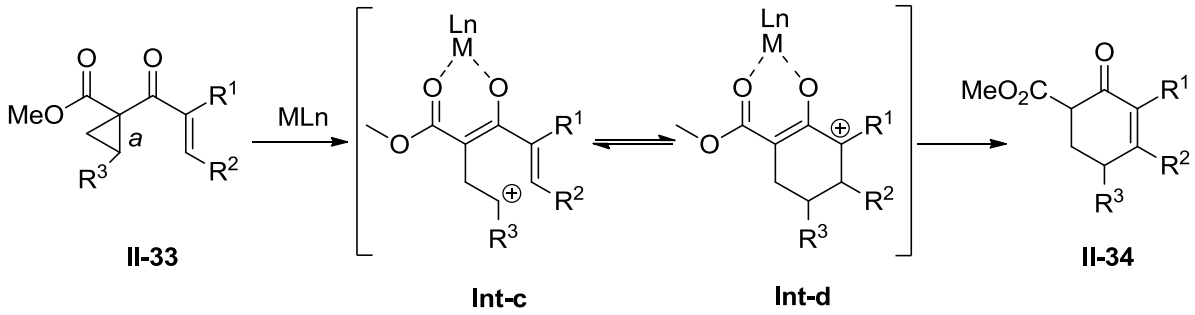


Figure 2.17. Proposed Reaction Design for the Formal Homo-Nazarov Cyclization

2.4.2. MODEL SUBSTRATE SYNTHESIS

To test the rationale of using D-A-A cyclopropanes to promote catalysis, we set out to probe the reactivity of alkenyl cyclopropyl substrates. We chose to begin our investigation using a model substrate bearing an α-alkyl substituent and electron-rich aryl substituent on the cyclopropane. This substrate was chosen for initial examination due to the concerns about the stability of the resulting oxyallyl cation as compared to that of the benzylic cation (Figure 2.18). Thus, requisite alkenyl substrate **II-33a** was synthesized in three steps starting from the malonate derived Weinreb amide **II-35.** The amide **II-35** was transformed into the diazo species, which upon subsequent Rh-catalyzed cyclopropanation with 4-methoxystyrene yielded cyclopropyl Weinreb amide **II-36a**.

Finally, the addition of a Grignard nucleophile afforded alkenyl cyclopropyl ketones in good yields.

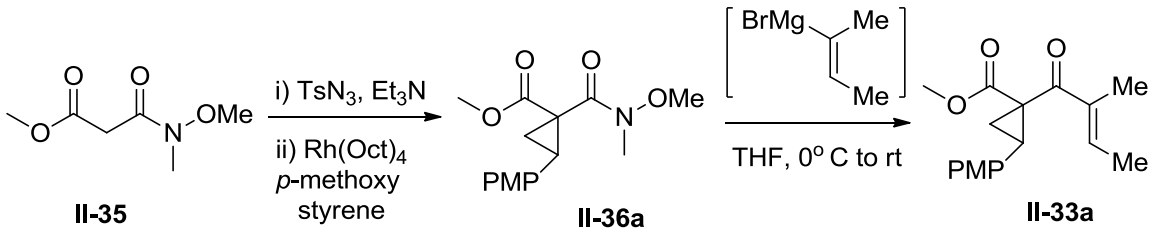


Figure 2.18. Synthesis of Model D-A-A Formal Homo-Nazarov Substrate

2.4.3. PROOF OF PRINCIPLE

With model substrate in hand, the initial reaction with **II-33a** was conducted in dichloromethane at room temperature in the presence of 30 mol % $Sc(OTf)_3$ as a Lewis acid promoter (Figure 2.19). The reaction progress was monitored by TLC and the reaction showed complete disappearance of starting material in less than 50 min. The crude ^1H NMR was taken using an aliquot of the reaction mixture. As anticipated, the cyclization predominantly afforded the cyclohexenone **II-34a** based on a formal homo-Nazarov-type eliminative pathway. Furthermore, we were intrigued to find another putative formal homo-Nazarov product, a cross-conjugated enol system with an exocyclic alkene **II-37a**. Beyond these two products, dihydrofuran **II-38**, which presumably arises from the enolate attack upon the acyclic benzylic cation, was observed (Figure 2.20). The reaction afforded **II-37a** and **II-34a** with a combined yield of 70%, accompanied by ~30% of dihydrofuran product (crude yields).

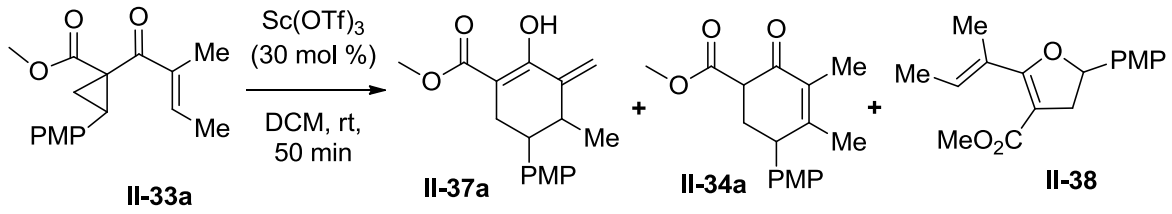


Figure 2.19. Test Reaction of Alkenyl Cyclopropyl Ketones with $Sc(OTf)_3$

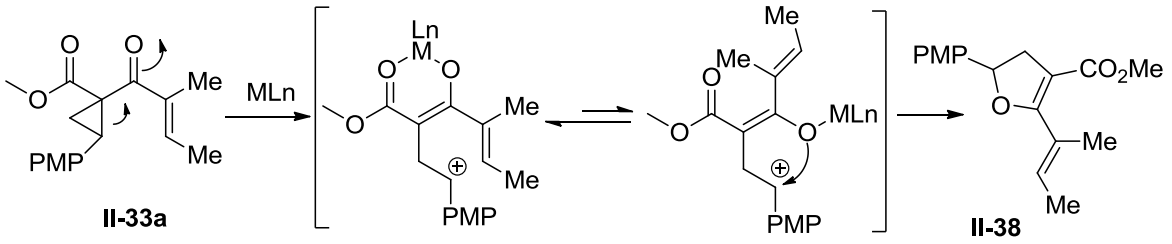


Figure 2.20. Proposed Mechanism for the Formation of Dihydrofuran Product

2.4.4. REACTION OPTIMIZATION

With substrates in hand, it was imperative to identify conditions that allowed for the successful formal homo-Nazarov cyclization of the alkenyl cyclopropyl ketones **II-33**. Based on preliminary results from the $Sc(OTf)_3$ reaction, a thorough Lewis acid screening was performed using substoichiometric amounts of various metal catalyst, primarily focusing on readily available triflate salt. Each reaction was performed using **II-33a** with 30 mol% Lewis acid salt in dichloromethane at room temperature. The reaction progress was monitored by TLC. Each reaction was stirred from 1 h up to a maximum time of 105 h. An aliquot of the reaction mixture was concentrated and a crude ^1H NMR was for each reaction. Based on the crude ^1H NMR spectra of the individual screening reactions, the ratios of formal homo-Nazarov products **II-34a** and **II-37a** were compared directly against those of **II-33a** and **II-38a** (Figure 2.21)**.** To our satisfaction, $In(OTf)_3$ emerged as the most efficient promoter (full conversion of **II-33a**

to **II-34a** and **II-37a** within 3 h), while $Zn(OTf)_2$ and $Cu(OTf)_2$ were the next best Lewis acids, although neither gave full conversion of **II-33a** even after 105 h. Pd(0) and Pd(II) complexes did not give any formal homo-Nazarov products.

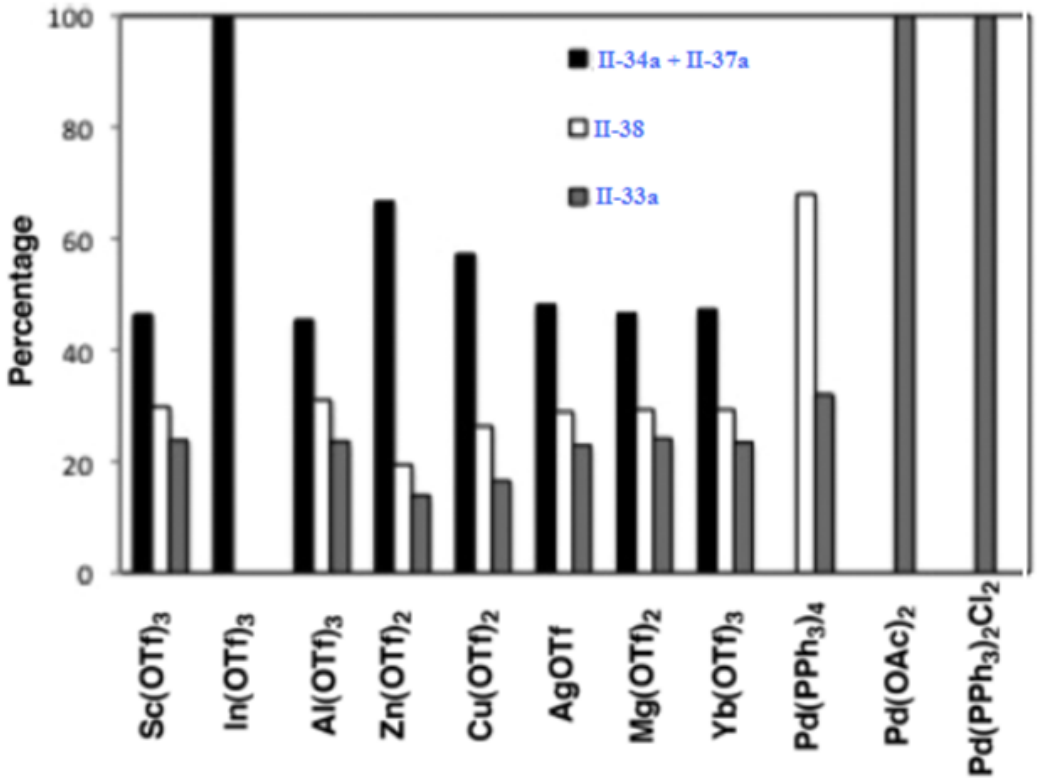


Figure 2.21. Results of Lewis Acid Screen for Alkenyl Cyclopropyl Ketones

Next, the effect of solvent on product outcome was examined. These experiments showed that the reactivity of substrate **II-33a** is strongly dependent on the nature of the solvent. Of the solvents screened, acetonitrile, THF, and nitromethane afforded relatively lower yields and thus were less promising. However, good yields were obtained in aromatic and halogenated solvents, indicating that the reaction progresses very smoothly in non-coordinating solvents. Of the solvents investigated, dichloromethane remained the

best choice and no observable changes in the product distribution were observed with any other solvents (Table 2.1).

Table 2.1. Influence of Solvents on the Reaction Outcome

entry	solvent	time	% yield[b] (**II-34a**+**II-37a**)	% yield[b] (**II-38**)
1	dichloromethane	40 min.	75	<1
2	1,2-dichloroethane	50 min.	72	<1
3	benzene	1 h	70	<1
4	nitromethane	1 h	65	<1
5	acetonitrile	5 h	40	<1
6	tetrahydrofuran	105 h	55	<5

[a] Reactions run with 1 equiv of substrate **II-33a** and 30 mol % $In(OTf)_3$ in solvents at 25 °C and complete within 1 h. [b] Percentages are based on product ratios calculated from crude ^1H NMR spectra for each individual reaction.

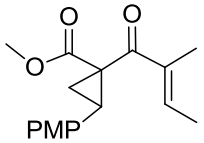
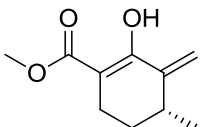
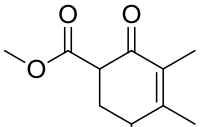
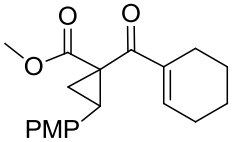
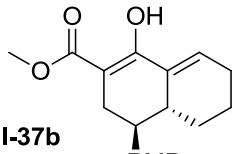
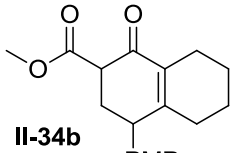
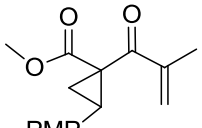
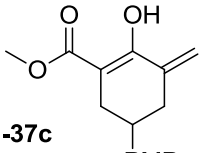
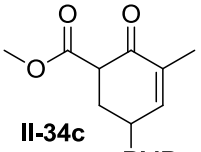
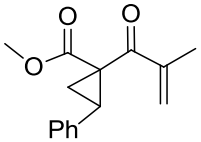
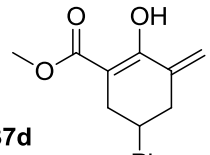
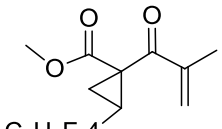
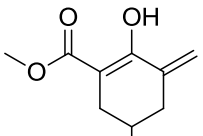
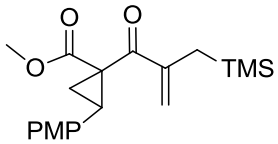
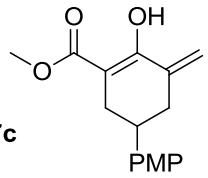
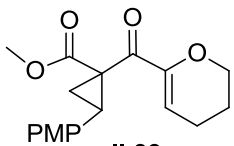
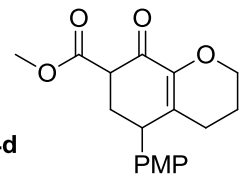
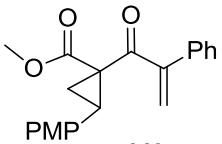
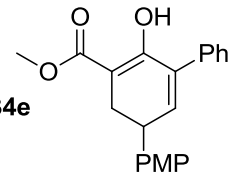
2.4.5. EXAMINING THE REACTION SCOPE AND LIMITATIONS

Having identified that 30 mol% $In(OTf)_3$ in dichloromethane at room temperature was the best overall catalyst system to promote the formal homo-Nazarov cyclization reaction of **II-33**, a diverse set of alkenyl cyclopropyl ketone substrates were screened to determine the reaction scope and applicability. When α-alkyl substrates are subjected to the reaction conditions, mixtures of **II-34** and **II-37** are observed. Model substrate **II-33a** provided the cyclohexene derivative **II-34a** and cyclohexenol product **II-37a** in 75% yield as a 1.5:1 mixture (Table 2.2, entry 1). For **II-37a**, the methyl group and phenyl were found to be orienting in a *trans* relationship (5:1 trans/cis *dr*) as confirmed by NMR.

Similarly, cyclohexenyl based ketone **II-33b** also proved to be a good substrate, affording products **II-34b** and **II-37b** in 1.5:1 mixture with a combined yield of 75% (Table 2.2, entry 2). With ketone **II-33c**, both products **II-34c** and **II-37c** were formed in a combined yield of 77% yield as a 1.5:1 mixture (Table 2.2, entry 3). Electron deficient aryl substituted cyclopropyl ketones proved to be more challenging than those that were electron rich. For example, cyclopropanes substituted with phenyl or 4-fluorophenyl (Table 2.2, entries 4 and 5), **II-37d** and **II-37e** were the only cyclized products observed in 46% (80% BRSM) and 56% yields (77% BRSM), respectively. The reactions did not go to completion even after 24 h, only offering starting material **II-33**. These observations can be rationalized based on the decreased cation stabilizing ability of the phenyl and 4-fluorophenyl groups in comparison to the strongly donating 4-methoxyphenyl group. Inspired from the pioneering work of Denmark and coworkers on silicon-directed Nazarov reactions,[36] a silyl group on the α-substituent of **II-33f** was installed to further stabilize the resulting oxyallyl cation. An allyl silane group to would also serve to enhance the nucleophilicity of the double bond and favor cyclization with a potentially altered product ratio. Gratifyingly, upon submitting silyl ketone **II-33f** to the optimized conditions, the reaction proceeded rapidly to form product **II-37c** in 92% yield within 0.5 h (Table 2.2, entry 6). The regioselectivity of the double bond formation in **II-37c** was completely governed by the elimination of the silyl group. The formation of this product also agrees with the mechanistic hypothesis of carbocation formation due to the *β*-silyl effect. To further increase the versatility of our formal homo-Nazarov process, it was decided to test substrate derived from dihydropyran. This was chosen for two reasons: 1) reaction would furnish bicycylic pyran-fused cyclohexenones as a product; 2)

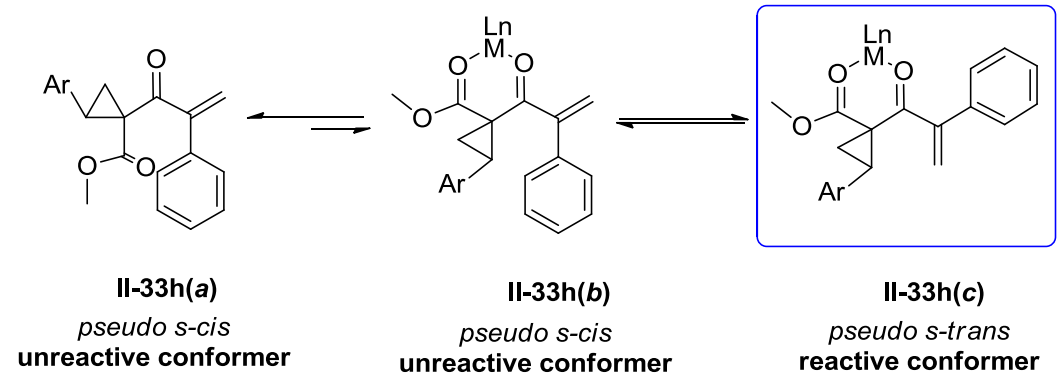
a pyranyl heteroatom ring would govern the regioselectivity of the double bond formation in the product. As anticipated, the cyclization of dihydropyran based ketone **II-33g** proceeded efficiently providing **II-34d** as the only observable product in 93% yield (Table 2.2, entry 7). Finally, we inspected a substrate bearing a α-phenyl group (Table 2.2, entry 8). We anticipated that the introduction of α-phenyl group would promote reactivity both by favoring the formation of the reactive *pseudo s-trans* conformation **II-33h(*c*)** and further stabilizing the resulting cyclic oxyallyl cation (Figure 2.22). By avoiding any potential unfavorable steric interactions in the *pseudo s-cis* conformation **II-33h(*a*)**, α-phenyl substitution favors σ-bond rotation to populate the reactive conformer **II-33h(*c*)**, which affords the correct geometry for cyclopropane ring-opening and subsequent ring-closure in the formal homo-Nazarov cyclization. Also, an electron-withdrawing group (i.e. FG = ester) in this position has the potential to bind a Lewis acid in a bidentate fashion, further promoting the reactive *pseudo s-trans* conformation. When **II-33h** (bearing a α-phenyl substituent) was subjected to the reaction conditions, only 30% yield (50% BRSM) of the expected cyclized product **II-34e** was observed after 35 h. Along with unreacted starting material, the major component was the dihydrofuran by-product. This marks the only instance in which this by-product is observed when $In(OTf)_3$ is used as the Lewis acid promoter. This can be rationalized if **II-33h** exists in the less reactive *pseudo s-cis* enone conformation. MMFF calculations revealed that the *pseudo s-cis* conformation **II-33h(*a*)** is more stable than the *pseudo s-trans* conformation **II-33h(*c*)** by more than 6 kcal/mol due to the presence of stabilizing π-interactions between the α-phenyl substituent and the oxygen lone pairs of the adjacent ester group.

Table 2.2. Scope of Homo-Nazarov Cyclization of Alkenyl Cyclopropyl Ketones[a]

entry	substrate	product (*s*)	(% yield)[b]
1	 **II-33a**	 **II-37a** (45%)	 **II-34a** (30%)
2	 **II-33b**	 **II-37b** (45%)	 **II-34b** (30%)
3	 **II-33c**	 **II-37c** (46%)	 **II-34c** (31%)
4[c]	 **II-33d**	 **II-37d** (46%)[d]	
5[c]	 **II-33e**	 **II-37e** (55%)[d]	
6	 **II-33f**	 **II-37c** (92%)	
7	 **II-33g**	 **II-34d** (93%)	
8	 **II-33h**	 **II-34e** (29%)[d]	

[a] Reactions run with 1 equiv of substrate **II-33** and 30 mol % $In(OTf)_3$ in DCM at 25 °C and complete within 1 h. [b] Isolated yields after column chromatography. [c] Reaction did not go to completion over 24 h. [d] Yields based on recovered starting material are as follows: **II-37d** (80%); **II-37e** (77%); and **II-34e** (50%).

Consequently, upon cyclopropane ring-opening, enolate trapping of the acyclic cation directly outpaces the formal homo-Nazarov cyclization pathway due to the difficulty in rotating into the more reactive *pseudo s-trans* enone conformer.



II-33h(*a*)
pseudo s-cis
unreactive conformer

II-33h(*b*)
pseudo s-cis
unreactive conformer

II-33h(*c*)
pseudo s-trans
reactive conformer

Figure 2.22. Steric Impact of Phenyl Substitution Alpha to the Ketones

2.4.6. DERIVATIZATION OF PRODUCTS

As a further illustration of the utility our formal homo-Nazarov cyclization of alkenyl cyclopropyl ketones, alkenyl products were used as synthetic building blocks by converting them into other useful compounds (Figure 2.23). For instance, when **II-37c** was treated with thiophenol, thioether **II-39** was obtained in 58% yield as a 1:1 mixture of diastereomers. Similarly, **II-34a** was subjected to Krapcho decarbalkoxylation conditions to generate **II-40** in 74% yield.

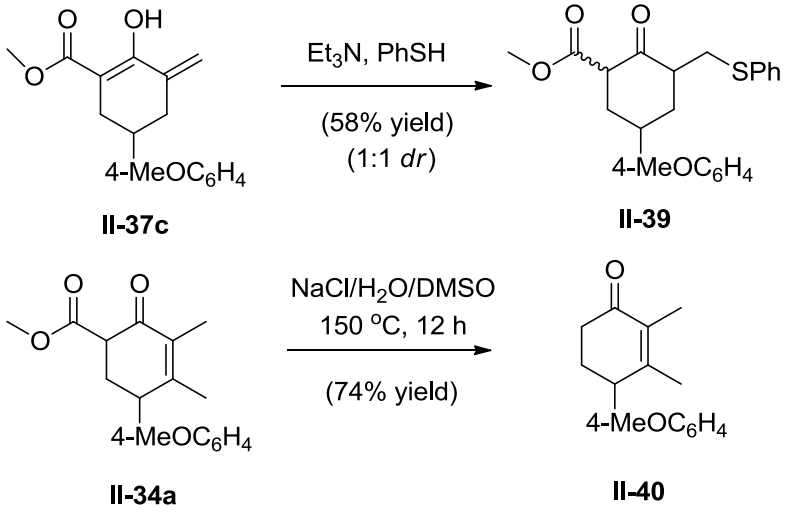


Figure 2.23. Facile Derivatization of the Formal Homo-Nazarov Cyclization Products

2.5. FORMAL HOMO-NAZAROV CYCLIZATION OF CYCLOPROPYL HETEROARYL KETONES[‡]

2.5.1. INTRODUCTION AND BACKGROUND

The acid-catalyzed ring closure of heteroaryl vinyl ketones to heteroaromatic ring-fused cyclopentanones is referred as the heteroaromatic Nazarov cyclization.[37] Analogous to this, an acid-catalyzed transformation of a cyclopropyl heteroaryl ketone into a heteroaromatic ring-fused cyclohexanone would constitute a homologous variation of above reaction and thus may be referred as the heteroaromatic formal homo-Nazarov cyclization (Figure 2.24). A viable approach to generate heteroaryl fused skeletons remained sparsely explored even today, with prior appearance in only three literature reports.

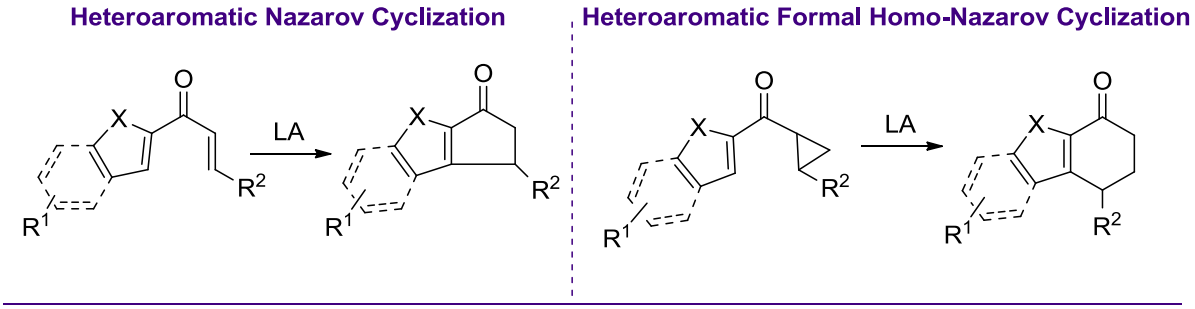


Figure 2.24. Heteroaromatic Nazarov vs Heteroaromatic Formal Homo-Nazarov Cyclization

[‡] This work was performed in collaboration with Lien H. Phun and Marchello A. Cavitt, fellow graduate students in the France research group.

In 2005, Otto and co-workers disclosed the first report on the homo-Nazarov cyclization of heteroaryl substituted cyclopropyl ketones to generate the [*b*]annelated cyclohexenones.[38] When 2-furanyl- and 2-thienyl cyclopropyl ketones **II-41** were reacted with $SnCl_4$, and subsequent acidic work-up, ketones furnished the desired ring-fused cyclohexenone derivatives **II-42** with yields of 94% and 54% respectively. However, when the reactions were performed on an identical substrate but with subsequent work-up under basic condition, ketones furnished hydroxyl products **II-43** in 40-70% yields (Figure 2.25).

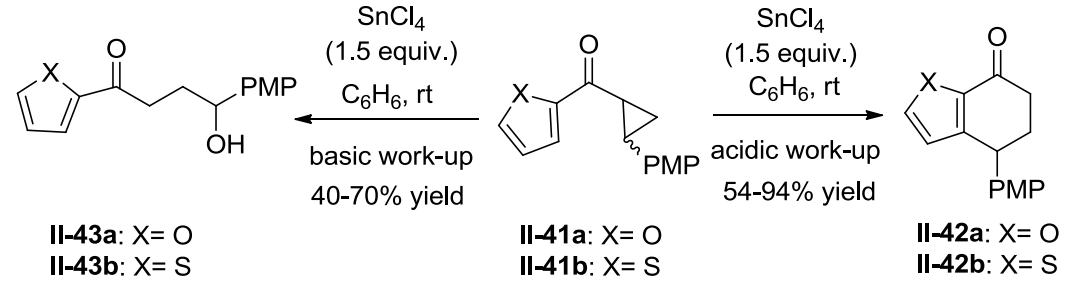


Figure 2.25. Otto's Heteroaromatic Formal Homo-Nazarov Cyclization

The scope of heteroaromatic formal homo-Nazarov cyclization was greatly expanded by Yadav and co-workers in 2008.[39] The reaction of heteroaryl 2-silylmethyl substituted cyclopropanes in the presence of 4 equiv. $SnCl_4$ in 1,2-dichloroethane at 80^oC furnished 2,3-heteroaromatic ring-fused 4-silylmethyl substituted cyclohexanones. Several 2- or 3-substituted furanyl, thienyl, and indolyl ketones **II-44a** (or **b**) efficiently cyclized to provide corresponding products **II-45a** (or **b**) in good to high yields. Yadav elegantly utilized a bulky silyl group to stabilize the carbocationic intermediate formed upon ring-opening (Scheme 2.26). More importantly, this work also reported first example of an oxygen substituent derived from dihydrofuran as a donor group on

cyclopropane **II-44c** in formal homo-Nazarov chemistry to generate tricyclic product **II-45a**.

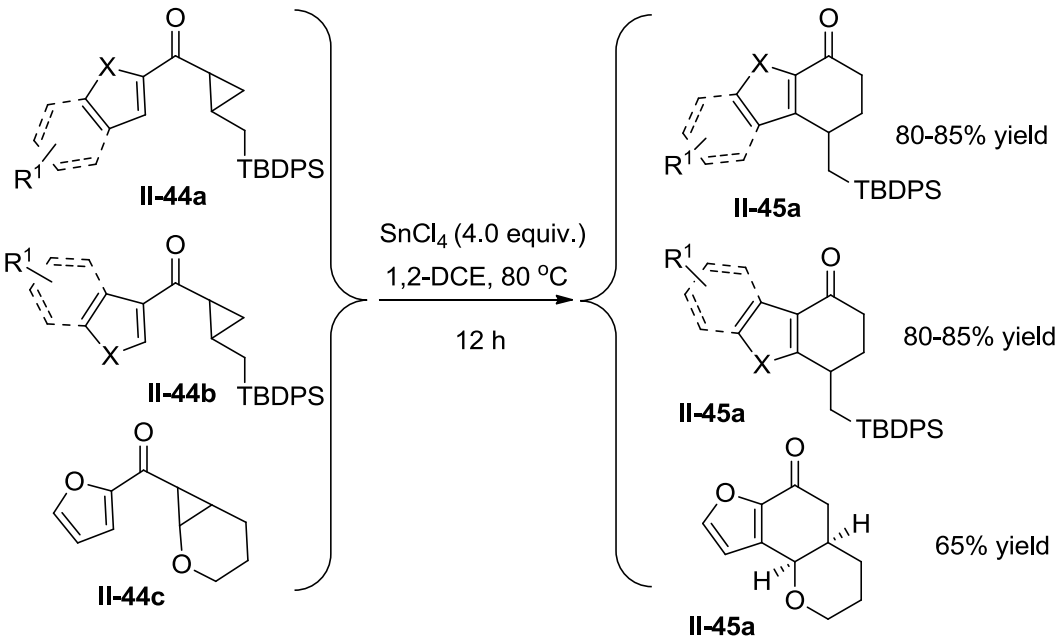


Figure 2.26. Yadav's Heteroaromatic Formal Homo-Nazarov Cyclization

More recently, the Waser group reported a catalytic formal homo-Nazarov cyclization of activated vinyl cyclopropyl ketone using *p*-TsOH.[34] In this report, Waser disclosed the successful cyclization of only one heteroaryl substrate **II-46** derived from 2-subsituted indole to generate tricyclic cyclohexanone product **II-47** quantitative yield (Figure 2.27).

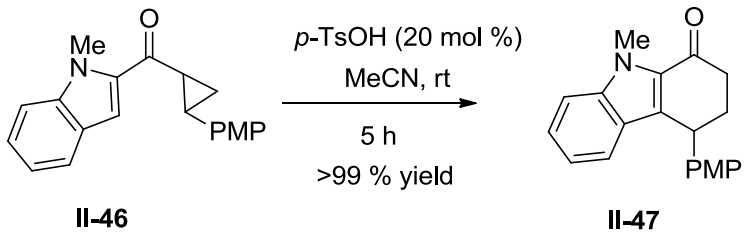


Figure 2.27. Waser's Heteroaromatic Formal Homo-Nazarov Cyclization

All of these reports suffer from one or more major limitations: 1) use of huge excess of Lewis acids; 2) harsh reaction conditions-use of elevated temperature; 3) generality of the reaction; and 4) tolerance to a wide range of functionality. Thus, a need remains for a general heteroaromatic formal homo-Nazarov cyclization protocol that will generate heteroaromatic ring-fused cyclohexanones more efficiently in high-yields and under mild conditions. In the following sections of this chapter, $In(OTf)_3$-catalyzed cyclization of heteroaryl cyclopropyl ketones that allows for the synthesis of heteroaromatic ring-fused cyclohexanone compounds will be discussed.

2.5.2. REACTION PROPOSAL

In 2010, the France lab developed a $In(OTf)_3$-catalyzed efficient formal homo-Nazarov cyclizations of alkenyl cyclopropyl ketones to generate cyclohexenones and methylene cyclohexanols under mild conditions.[40] More importantly, our report utilizes cyclopropane bearing a secondary electron acceptor (an ester group) for the first time in homo-Nazarov chemistry. The introduction of an acceptor group markedly changed the reactivity of the cyclopropyl ketone substrates allowing cyclopropyl ring-opening under catalytic amount of the Lewis acid promoter in DCM at room temperature. With this concept in mind, the France group began examining additional heteroaromatic structures that might be targeted using our donor-acceptor-acceptor (D-A-A) based formal homo-Nazarov approach. The France and coworkers postulated that by replacing the unactivated vinyl group of the alkenyl cyclopropyl ketones previously used in the synthesis of cyclohexenones and methylene cyclohexanols with an electron-rich heteroaromatic group as reactive π-systems **II-48** capable of attacking cationic

intermediate generated upon cyclopropane ring-opening, a synthesis of heteroaromatic ring-fused cyclohexanones **II-49** could be achieved (Figure 2.28). If successful, this would open avenues to the convergent assembly of an even wider class of natural products and medicinally active molecule targets.

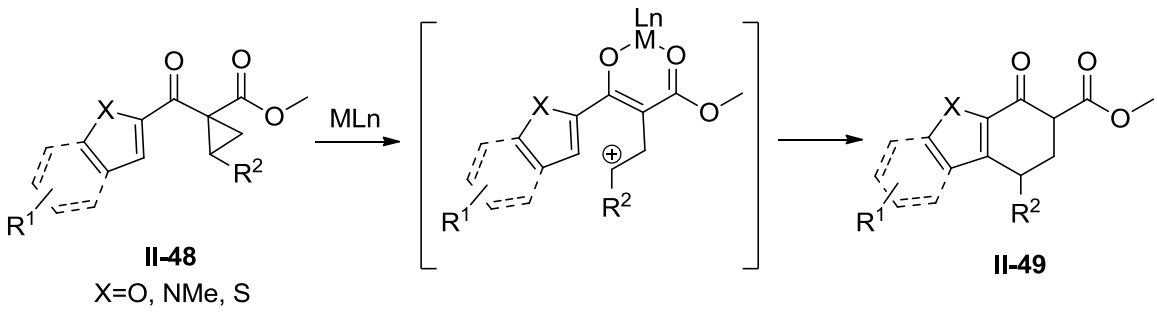


Figure 2.28. Proposed Heteroaromatic Formal Homo-Nazarov Cyclization

2.5.3. SUBSTRATE SYNTHESIS

To begin our investigations, a variety of 2- and 3-heteroaryl substituted cyclopropyl ketone substrates were synthesized. Synthesis of the appropriate cyclopropyl ketones was achieved in three steps starting from readily available 2- or 3-substitued heteroaromatic acid chloride. Addition of *in-situ* prepared lithium 1-methoxyethenolate species to the appropriate 2- or 3-substituted heteroaromatic acid chloride generated β-ketoesters **II-50**. Subsequent diazo transfer reaction then furnished α-diazoesters **II-51**. Finally, Rh(II)-catalyzed cyclopropanation in the presence of the requisite alkenes provided cyclopropyl ketones **II-48** as the heteroaromatic formal homo-Nazarov precursors (Figure 2.29).

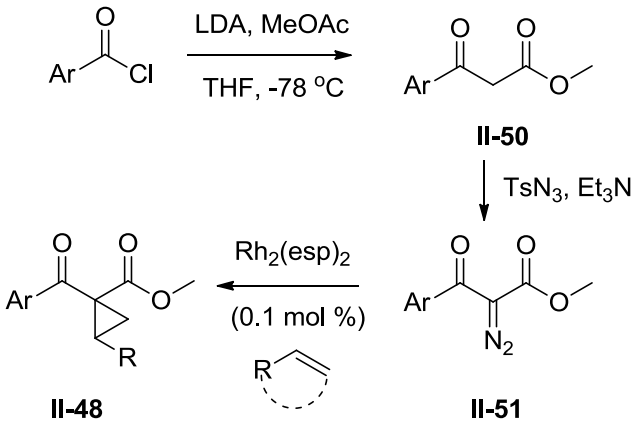


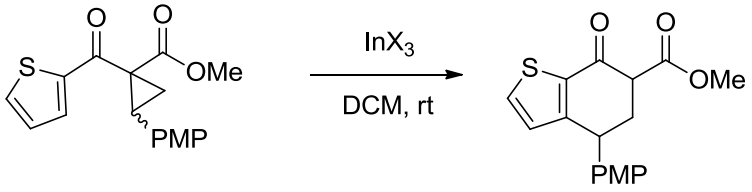
Figure 2.29. Synthesis of Heteroaromatic Formal Homo-Nazarov Precursors

2.5.4. INITIAL STUDIES

Our initial investigations focused on cyclopropyl ketone substrate derived thiophene 2-carboxylic acid. This substrate was chosen for optimization of our protocol due to thiophene's stability in the presence of Lewis acids and proven success as a promising substrate in the heteroaromatic Nazarov cyclization reaction.[37] The initial work began by examining the conditions previously used in the France lab to promote alkenyl formal homo-Nazarov cyclization. The 2-thienyl substrate **II-48a** was treated with 30 mol% $In(OTf)_3$ in dichloromethane at room temperature. To our delight, this initial attempt produced the desired cyclohexanone **II-49a** in 88% yield, thereby confirming the feasibility of our D-A-A based heteroaromatic formal homo-Nazarov cyclization approach to heteroaryl ring-fused cyclohexanones (Table 2.3, entry 1). Next, the effect of lowering the amount of catalyst was examined. Treatment with 5 mol% and 1 mol% of $In(OTf)_3$ promoted formation of the desired products in 86% and 77% respectively (Table 2.3, entry 2 and 3). As anticipated, the reaction time gradually increased as the catalyst loading lowered. When the reaction was performed using 5 mol % of $InCl_3$, cyclization

was observed which was comparable in time to $In(OTf)_3$ with a significant decrease in yield (Table 2.3, entry 4). Influenced by successful use of $LiClO_4$ as an additive in $Sc(OTf)_3$- and $In(OTf)_3$-catalyzed Friedel-Crafts acylations,[41] and Nazarov cyclizations,[35,37] $LiClO_4$ salt was examined. When 1 equiv. of $LiClO_4$ was used with either In^{3+} salt, disappointingly both reactions resulted in poor conversions. Thus, 5 mol % $In(OTf)_3$ in dichloromethane at room temperature remained as the optimal reaction condition.

Table 2.3. Effects of Catalyst Loading on the Reaction Outcome



entry	Lewis acid	catalyst loading (mol%)	time (h)	% yield
1	$In(OTf)_3$	30	2.5	88%
2	$In(OTf)_3$	5	5	86%
3	$In(OTf)_3$	1	6.5	77%
4	$InCl_3$	5	4.5	78%

2.5.5. REACTION SCOPE EXAMINATION

Having identified the optimal reaction conditions, the scope of this reaction was examined by subjecting a series of 2- or 3-substituted heteroaryl cyclopropyl ketones under identical conditions. The 3-thienyl substrate **II-48c** was found to produce the expected cyclohexanone product in 73% yield, lower than 2-thienyl cyclopropane **II-48a**

which afforded **II-49a** in 86% yield (Table 2.4, entry 1 and 3). When 3-furanyl substrate **II-48d** was reacted, it generated corresponding product **II-49d** in 73% yield (entry 4). However, its 2-furanyl counterpart **II-48b** readily cyclized at room temperature furnishing product **II-49b** in only 28% yield. The observed lower yields were attributed to the formation of several by-products. To attenuate this issue, **II-48b** was refluxed in 1,2-DCE. Interestingly, subjecting to 1,2-DCE reflux, the reaction afforded its product **II-49b** in 67%, and no side product formation was observed (entry 2). The higher temperature probably allows the 2-substituted furanyl substrate to achieve the requisite transition state that leads to the productive pathway. The success with the 2-substituted furanyl and thienyl substrates is indeed noteworthy, since the general observation of the literature examples clearly indicates that an electrophilic substitution at 3-position is less facile than an electrophilic substitution at 2-position in heteroaromatic compounds except the indoles. The 2- and 3-substituted indolyl cyclopropanes **II-48e** and **II-48g** generated the desired products **II-49e** and **II-49g** in 63% and 61% yields, respectively (entries 5 and 7). Similarly, the 2- and 3-substituted benzofuranyl precursor's cleanly cyclized to give **II-49f** and **II-49h** in 91% and 71% yields respectively (entry 6 and 8). This result is notable because benzofuran derived substrates had been unsuccessful as a formal homo-Nazarov substrate due to competing polymerization issues. The successful reaction of **II-48g/h** demonstrates a remarkable ring-closing efficiency of the heteroaromatic formal homo-Nazarov protocol.

To further expand the scope of this reaction in constructing other highly substituted heteroaryl ring-fused cyclohexanones, we examined a 3-substituted substrate with the 2-position blocked, as in the 2-bromo thienyl cyclopropane **II-48i**. With the 2-

position unavailable, the only site for the electrophilic substitution would be the 4-position. If successful, this would yield the 3,4-fused heteroaryl cyclohexanone **II-49i**. As envisaged, the reaction of **II-48i** generated the desired cyclization product **II-49i** in 56% yield (entry 9). This synthesis of 3,4-fused systems is reported for the first time in homo-Nazarov chemistry as it mainly generates only 2,3-ring-fused heteroaromatics. Next, the effect of donor substituents about cyclopropane on reactivity was investigated (Table 2.5). The phenyl derivatives **II-48j** and **II-48k** did not cyclize efficiently under optimized conditions. To alleviate this issue, the substrates were subjected to heating in 1,2-dichloroethane at 80^{o}C, to afford the desired ring-fused products **II-49j** and **II-49k** in 81 and 83% yield respectively(entry 1 and 2). When the α-methyl styrene-derived 2-thienyl cyclopropane **II-48l** was treated with $In(OTf)_3$ at room temperature, the reaction proceeded smoothly to generate product **II-49l** in 71% yield (entry 3), whereas the phenyl derivative **II-48j** did not cyclize at room temperature. Thus, with the introduction of a methyl group geminal to the phenyl a strong accelerating effect was observed. A plausible explanation would be a faster ring-opening of the cyclopropane ring due to release of steric strain and higher stability of the resulting tertiary benzylic carbocationic intermediate. Similarly, the indanyl substrate **II-48m** gave tetracycle **II-49m** in 87% yield (entry 4). Encouraged by Yadav's recent work on the successful use of a silylmethyl group and oxygen substituent as a donor group on the cyclopropanes, silyl derivative **II-48n** and dihydropyran derivative **II-48o** was synthesized. The reaction with silylmethyl derivative afforded product **II-49n** in 72% yield (entry 5). Disappointingly, no cyclization occurred when dihydropyran derivative was subjected to the reaction

conditions. Even at higher catalyst loadings or elevated temperatures, only starting material was recovered (entry 6).

This lack of reactivity can be rationalized if no chelation event was occurring at the two carbonyls (Figure 2.30). To support this postulation, MMFF calculations were performed for the lowest energy conformers of **II-48o**. In each of these conformers, the two carbonyl oxygens are found to be anti to one another, thus eliminating the two-point chelation to the Lewis acid. Without this activation, cyclopropane ring-opening does not occur. Additionally, this effect seems to arise from the stereoelectronic influence of the methyl ester on the conformation of the fused pyran ring. This effect can arguably be seen in the ^{1}H NMR spectrum of **II-48o** where the hydrogen at the fused ring junction adjacent to the oxygen is located at 6.5 ppm, which represents a ~3 ppm downfield shift from the analogous pyranyl derivative without the ester. This downfield shift suggests the strong influence of the electron-withdrawing ester on the conformation of the fused ring.

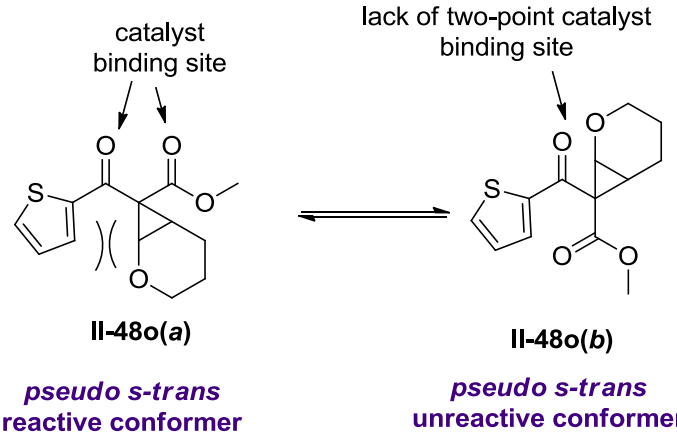
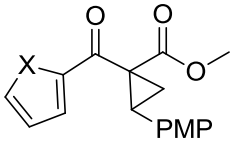
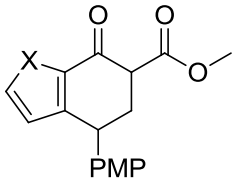
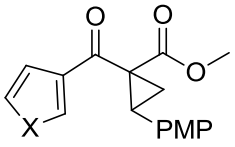
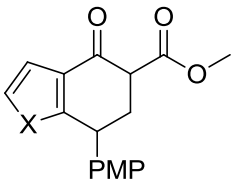
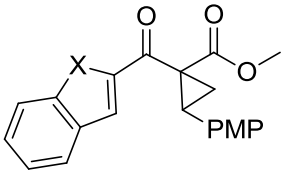
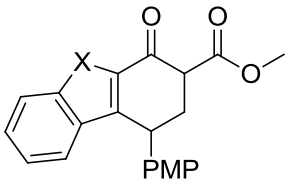
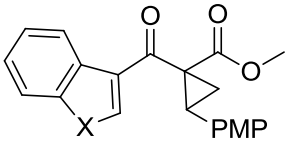
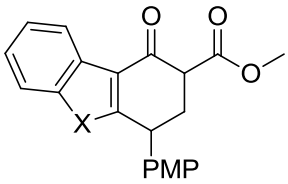
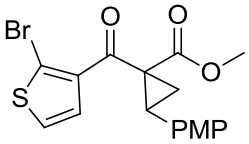
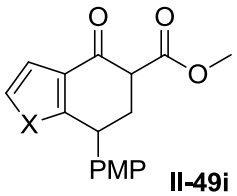


Figure 2.30. Proposed Lowest Energy Conformer of **II-48o**

Table 2.4. Scope of Heteroaryl Substituents on the Reaction[a]

entry	substrate	product	% yield[b]	dr *(cis:trans)*[c]
				
1	**II-48a: X=S**	**II-49a: X=S**	86%	1.5:1
2[d]	**II-48b: X=O**	**II-49b: X=O**	67%	1.1:1
				
3	**II-48c: X=S**	**II-49c: X=S**	73%	1.7:1
4	**II-48d: X=O**	**II-49d: X=O**	73%	1.1:1
				
5	**II-48e: X=NMe**	**II-49e: X=NMe**	63%	1.2:1
6	**II-48f: X=O**	**II-49f: X=O**	91%	1.4:1
				
7	**II-48g: X=NMe**	**II-49g: X=NMe**	61%	1.2:1
8	**II-48h: X=O**	**II-49h: X=O**	71%	1.2:1
9	 **II-48i**	 **II-49i**	56%	----[e]

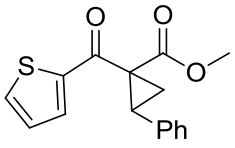
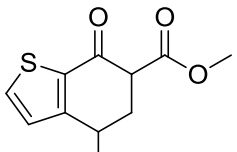
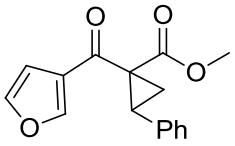
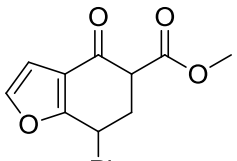
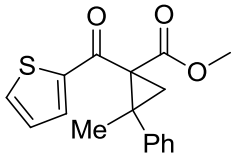
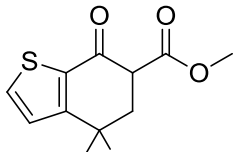
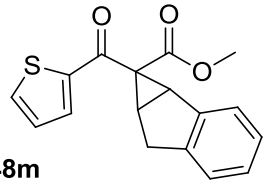
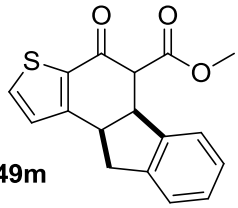
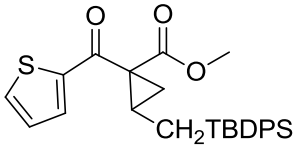
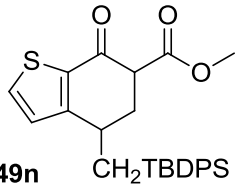
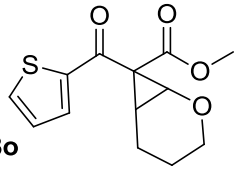
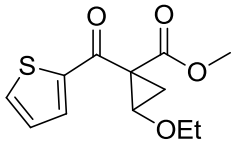
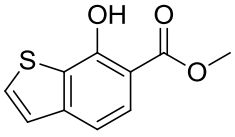
[a]Reactions run with 1 equiv of substrate **II-48** and 5 mol% $In(OTf)_3$ in DCM at 25 °C [b]Isolated yields after column chromatography. [c]Diastereoselectivities as determined by crude ^1H NMR. [d]Reaction performed in 1,2-dichloroethane at 80 °C. [e]2:1 Mixture of keto and enol forms.

This may explain why substrate **II-48o** failed to cyclize, even after extended reaction times and high catalyst loadings. To test confirm hypothesis, the acyclic ether derivative **II-48p** (derived from ethyl vinyl ether) was synthesized. When **II-48p** was subjected to the standard reaction conditions, the cyclization occurred to provide the substituted benzothiophene **II-49p** in 51% yield (entry 7). The resulting product seemingly arises from a rapid aromatization of the transient formal homo-Nazarov cyclization product through an In(III)-induced elimination of EtOH. This result further supported our hypothesis.

2.5.6. ONE-POT PROCEDURE FOR FORMAL HOMO-NAZAROV REACTION

Having confirmed that this D-A-A based heteroaromatic formal homo-Nazarov cyclization was capable of constructing several substituted heteroaryl ring-fused cyclohexanones, the development of a one-pot protocol that would occur in the presence of both the rhodium (for cyclopropanation) and indium (for cyclization) catalyst was examined. If successful, this route would enable a convergent approach to the assembly of functionalized derivatives, from readily available starting materials, and ultimately increasing the synthetic utility of this reaction. To verify the feasibility of this approach, two key control reactions were performed. First, the stability of α-diazoester **II-51** in the presence of $In(OTf)_3$ (5 mol %) was established by monitoring a stirring mixture of the two components. Next, the stability of the alkene (4-methoxy styrene) was tested in the presence of both Rh_2esp_2 and $In(OTf)_3$.

Table 2.5. Effects of Cyclopropyl Substituents on the Reaction Outcome[a]

entry	substrate	product	% yield[b]	dr *(cis:trans)*[c]
1[d]	 **II-48j**	 **II-49j**	81%	2.3:1
2[d]	 **II-48k**	 **II-49k**	83%	1.2:1
3	 **II-48l**	 **II-49l**	71%	2:1
4	 **II-48m**	 **II-49m**	87%	---[e]
5	 **II-48n**	 **II-49n**	72%	2.4:1
6	 **II-48o**	no reaction	-----	----
7	 **II-48p**	 **II-49o**	51%	----

[a] Reactions run with 1 equiv of substrate **II-48** and 5 mol% $In(OTf)_3$ in DCM at 25 °C [b]Isolated yields after column chromatography. [c] Diastereoselectivities as determined by crude ^1H NMR. [d] Reaction performed in 1,2-dichloroethane at 80 °C. [e] Only one diastereomer visible by ^1H NMR

To achieve an active indium catalyst loading of ~20 mol%, 1 mol% of Rh_2esp_2 and 0.2 mol% of $In(OTf)_3$ in DCM at 0 ^oC were employed in the reaction. Gratifyingly, subjecting α-diazoester **II-51** to these conditions afforded the desired product **II-49d** in 56% yield, which is higher than the yield for the two-step procedure and equates to an average of about 75% yield for each individual step (Figure 2.31).

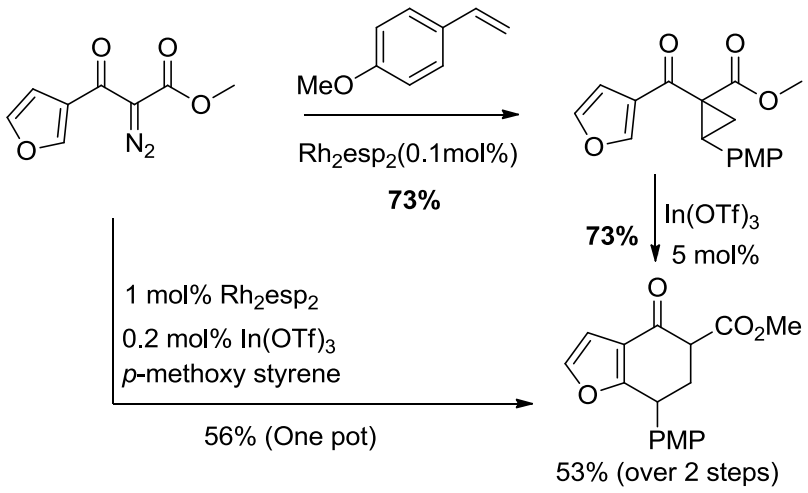


Figure 2.31. Example of Tandem Cyclopropanation/Formal Homo-Nazarov Cyclization

2.6. CONCLUSION

In conclusion, an efficient protocol for the formal homo-Nazarov cyclization of alkenyl cyclopropyl ketones was developed. We also demonstrated that by utilizing the donor-acceptor-acceptor cyclopropanes (D-A-A), a high-yielding cyclization reaction could be developed. Alkenes bearing hydrogens on an α-substituent (or silyl groups) provided 1.5:1 mixtures of methylene cyclohexenols and cyclohexenones. When no α-hydrogens (or silyl groups) are present, only cyclohexenone based products are observed. The products rapidly formed in good to high yields (up to 93%) under mild conditions and from readily available starting materials in only three steps. Finally, we have shown that homo-Nazarov cyclization products could be readily derivatized into useful building blocks. This method would find its application towards the natural product synthesis in the future.

A general protocol for the heteroaromatic formal homo-Nazarov cyclization has also been reported. This methodology provides rapid access to functionalized heteroaromatic ring-fused rings to cyclohexanones. The products are formed in good to excellent yields (56-91%) yields. Expanding this scope of this result, we have demonstrated the potential of transforming this two-step process in one-pot method. Therefore, this methodology could be used for the synthesis of natural products containing heteroaryl-ring fused cyclohexanones.

2.7. EXPERIMENTAL SECTION FOR FORMAL HOMO-NAZAROV CYCLIZATION OF ALKENYL CYCLOPROPYL KETONES

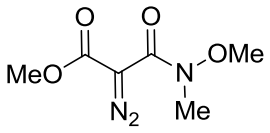
2.7.1. General Methods

Infrared (IR) spectra were obtained using a Nicolet 4700 FTIR with an ATR attachment from SmartOrbit Thermoelectronic Corporations and and are reported as cm-1 (w = weak, m = medium, s = strong, br = broad). Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Varian Mercury Vx 300 spectrometer with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, ddd = doublet of doublet of doublets, ddt = doublet of doublet of triplets, dtd = doublet of triplet of doublets, t = triplet, bt = broad triplet, td = triplet of doublets, q = quartet, qd = quartet of doublets, qn = quintet, m = multiplet), coupling constants (Hz), and integration. Mass spectra were obtained using a VG-70SE instrument. Chromatographic purification was performed as flash chromatography using Dynamic Adsorbents silica gel (32-65μm), using the solvents indicated as eluent with 0.1-0.5 bar pressure. For quantitative flash chromatography technical grades solvents were used. Analytical thin-layer chromatography (TLC) was performed on EMD silica gel 60 F_{254} TLC glass plates. Visualization was accomplished with UV light, aqueous basic potassium permanganate ($KMnO_4$) solution, iodine, aqueous acidic dinitrophenylhydrazine (DNP) solution, aqueous acidic *p*-anisaldehyde (PAA) solution, and ethanol solution of phosphomolybdic acid (PMA) followed by

heating. Yields refer to isolated yields of analytically pure material unless otherwise noted. All reactions were carried out in oven-dried glassware under an atmosphere of N_2, unless stated otherwise. Tetrahydrofuran and Diethyl ether were distilled from a sodium/benzophenone ketyl under N_2 and stored in a Schlenk flask. 1,2-dichloroethane and dichloromethane was purified by distillation from calcium hydride under N_2 prior to use. Acetonitrile was dried by fractional distillation over CaH_2. Benzene was purified by drying with CaH_2. Nitromethane was distilled over CaH_2 and stored under nitrogen under 4Å molecular sieves. All other reagents were purchased from Acros, Sigma-Aldrich, Fluka, VWR, Merck, Alfa Aesar, TCI and Strem (for metal catalysts) and used without further purification unless otherwise noted.

2.7.2. General Procedures

2.7.2.1. Formation of Diazo Reagent II-52

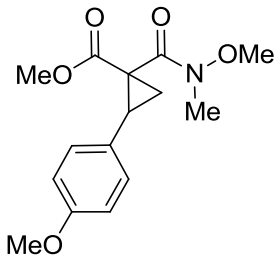


Diazo reagent **II-52** was prepared using a modified version of Charette's protocol:[42] A solution of *N*,*O*-dimethylhydroxylamine (3.35 g, 54.9 mmol) in dry DCM (10 mL) was added dropwise to a cold (0˚C) solution of methyl 3-chloro-3-oxopropanoate (5.00 g, 36.6 mmol) in dry DCM (50 mL) under nitrogen atmosphere. The resulting reaction mixture was stirred for 2 h at room temperature. Upon completion (as monitored by TLC), the mixture was concentrated under reduced pressure. The resulting residue was dissolved in 50 mL acetonitrile. To this β-amide ester, tosyl azide (10.8 g, 54.9 mmol, 1.5 equiv.) and triethylamine (7.41 gm, 73.2 mmol, 2.0 equiv.) were added.

The mixture was stirred at room temperature for 16 h then concentrated under reduced pressure. The resulting bright yellow/orange residue was purified by flash chromatography on silica gel using EtOAc/Hex (3:1) to give **II-52** as yellow oil.

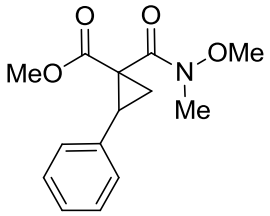
2.7.2.2. Formation of Racemic Cyclopropanes II-36a-c

A 100 mL flask was charged with $Rh_2(oct)_4$ (5 mol%) and a magnetic stir bar. The flask was purged with nitrogen. CH_2Cl_2 and the corresponding styrene (5.0 equiv.) were then added and the reaction was stirred at room temperature. The diazo reagent (1.0 equiv.) dissolved in CH_2Cl_2 was added to the reaction mixture over a period of 4 h using a syringe pump at 25˚C. After complete addition, the resulting mixture was stirred for an additional 30 h. The solvent was then removed under reduced pressure and the residue was purified by flash chromatography (100% hexane→15% EtOAc:hexane).

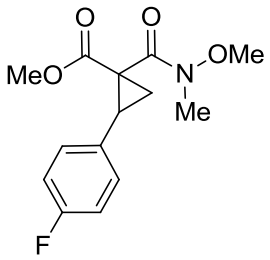


Methyl 1-(methoxy(methyl)carbamoyl)-2-(4-methoxyphenyl) cyclopropane carboxylate(II-36a). To a solution of 4-methoxystyrene (9.82 mL, 73.86 mmol, 5 equiv.) and $Rh_2(oct)_4$ (0.575 g, 5 mol %), and CH_2Cl_2 (60 mL) was added solution of diazoamide **II-52** (2.75 gm, 14.77 mmol, 1 equiv.) in CH_2Cl_2 (40 mL) over a period of 6 hours via syringe pump. Reaction progress was monitored by TLC. Reaction mixture was concentrated *in vacuo* after 30 hours, followed by purification via column chromatography (Hex→20% EtOAc/Hex) afforded cyclopropyl amide **II-36a** as an oil

(3.29 g, 76.0%). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 715.-6.94 (d, 2H, *J*=12Hz), 6.74 (dd, *J*=5.70, 5.12 Hz, 2H), 4.04-3.39 (m, 6H), 3.39-2.60 (m, 6H), 2.37-1.86 (m, 1H), 1.33 (m, 1H). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 167.8, 158.7, 130.1, 127.0, 113.5, 77.8, 77.4, 76.9, 61.4, 55.2, 52.1, 36.7, 17.6. **IR**: 3000.4(m), 2960.2(b), 2840.9(w), 2814.4(w), 1735.4(s), 1654.1(s), 1611.3(s), 1514.9(s) cm^{-1}. **HRMS(ESI)** M/Z+ Calc. 293.1363, Obs. 293.1273.



Methyl 1-(methoxy(methyl)carbamoyl)-2-phenylcyclopropanecarboxylate(II-36b). To a solution of styrene (3.07 mL, 26.85 mmol, 5 equiv.), $Rh_2(oct)_4$ (214.8 mg, 4 mol %), and CH_2Cl_2 (20 mL) was added solution of amide **II-52** (1.00 gm, 5.37 mmol, 1 equiv.) in CH_2Cl_2 (20 mL) over a period of 3 hours via syringe pump. Reaction progress was monitored by TLC. Reaction mixture was concentrated *in vacuo* after 30 hours, followed by purification via column chromatography (Hex→20% EtOAc/Hex) afforded cyclopropyl amide **II-36b** as an oil (862.5 mg, 62.0%). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.22 (m, 5H), 3.66 (s, 3H), 3.33 (s, 3H), 3.33-3.30 (m, 1H), 3.20 (s, 3H), 2.93-2.20 (dd, *J*=7.97, 4.94 Hz, 1H), 1.47 (dd, *J*=9.18, 4.94 Hz, 1H**). ^{13}C NMR** ($CDCl_3$, 75 MHz) δ 167.4, 134.8, 128.8, 127.8, 126.8, 61.2, 51.8, 36.6, 32.9, 28.6, 17.2. All NMR shifts match with reported values in the literature.



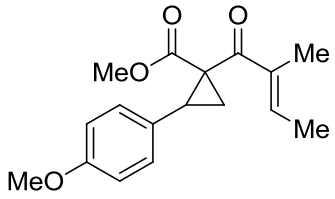
Methyl 2-(4-fluorophenyl)-1-(methoxy(methyl)carbamoyl)cyclopropanecarboxylate (II-36c). To a solution of 4-fluorostyrene (3.22 mL, 26.85 mmol, 5 equiv.) and $Rh_2(oct)_4$ (167.25 mg, 4 mol %), and CH_2Cl_2 (20 mL) was added solution of amide **II-52** (1.00 gm, 5.37 mmol, 1 equiv.) in CH_2Cl_2(20 mL) over a period of 3 hours via syringe pump. Reaction progress was monitored by TLC. Reaction mixture was concentrated *in vacuo* after 30 hours, followed by purification via column chromatography (Hex→20 % EtOAc/Hex) afforded cyclopropyl amide **II-36c** as an oil (815.7 mg, 54.0%). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.21-7.15(m, 2H), 6.96-6.85(t, 2H, *J* =6Hz, 6Hz), 3.65(s, 3H), 3.33(s, 3H), 3.30-3.22(m, 1H), 3.20(s, 3H), 2.20-2.10(q, *J* =3Hz, 3Hz, 3Hz, 3Hz), 1.40-1.50(q, *J* =3Hz, 3Hz, 3Hz, 3Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 167.5, 163.5, 120.3, 130.7, 130.6, 130.5, 130.4, 115.0, 114.7, 61.3, 52.0, 36.6, 33.1, 27.9, 17.4. **IR**: 3725.3 (m), 2949.8(m), 1733.9(s), 1652.9(s), 1604.1(m), 1558.1(s), 1511.6(s) cm^{-1}. **HRMS(ESI)** M/Z+ Calc. 281.1063, Obs. 281.1074.

2.7.2.3. Formation of Alkenyl Cyclopropyl Ketones II-33(a-h)

General Method A: A solution of Grignard reagent (1.5 equiv.) was added slowly to a stirred solution of Weinreb amide **II-36** in THF (10 mL) at -78˚C. The solution was stirred at this temperature for the indicated time, gradually warming to room temperature. The reaction was monitored by TLC. The solution was then quenched with saturated

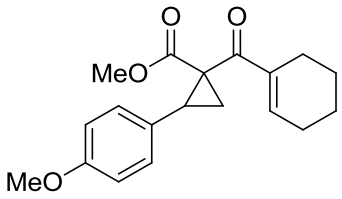
aqueous NH_4Cl (5 mL/mmol), extracted with Et_2O (3x10 mL/mmol of amide) and washed with brine (2x5 mL/mmol of amide), dried over $MgSO_4$ and concentrated under reduced pressure.

General Method B: Adapted from a reported procedure,[34] *t*-BuLi (1.7 M in pentane , 2.0 equiv.) was added dropwise in a solution of bromoalkene (2.2 equiv.) in THF (0.10 M) at -78˚C. The reaction mixture stirred at -78˚C for 30 min. The flask was then transferred to an ice bath (0˚C). After 30 min, the reaction was re-cooled to -78˚C and a solution of amide **II-36** (331 mg, 1.12 mmol, 1.0 equiv.) in THF (0.20M) was added slowly dropwise. The reaction was stirred at -78˚C for another 1 h, gradually warming to room temperature. The solution was then quenched with saturated aqueous NH_4Cl (5 mL/mmol), extracted with Et_2O (3x10 mL/mmol of amide) and washed with brine (2x5 mL/mmol of amide), dried over $MgSO_4$ and concentrated under reduced pressure.

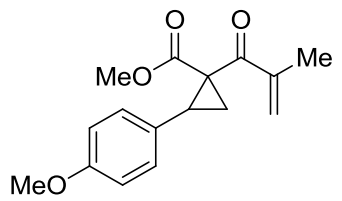


(*E*)-Methyl 2-(4-methoxyphenyl)-1-(2-methylbut-2-enoyl)cyclopropanecarboxylate (II-33a). Method A was followed using (*E*)-but-2-en-2-ylmagesium bromide (17.73 mL, 8.86 mmol, 0.5M in THF, 1.3 equiv.) and amide **II-36a** (2.0 g, 6.81 mmol, 1.0 equiv.). The reaction was quenched after 2 h to give **II-33a** (1.25 g, 64% yield) after purification via flash chromatography (1:6 EtOAc/Hex) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.14-7.06 (d, 2H, *J* =12Hz), 6.80-6.74 (d, 2H, *J* = 12 Hz), 5.64-5.56 (m, 1H), 3.72 (s, 3H), 3.42-3.38 (t, 1H, *J* = 9Hz, 3 Hz), 3.32 (s, 3H), 2.28-2.20 (dd, 1H, *J* = 4.88, 8.09 Hz), 1.90 (s, 3H), 1.78-1.70 (d, 3H, *J* =2.5 Hz), 1.68-1.62(dd, 1H, *J* =3 Hz, 6.3Hz).

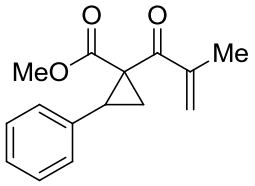
^{13}C NMR ($CDCl_3$, 75 MHz) δ 201.5, 195.7, 169.2, 168.5, 158.7, 158.5, 137.7, 137,6, 137.1, 133.4, 129.9,129.7, 128.6, 128.0, 127.2, 126.9, 126.6, 113.9, 113.4, 113.3, 83.1, 55.1, 55.0(2C), 52.0, 51.8, 50.8, 44.9, 41.3, 38.0, 33.8, 29.4, 22.0, 21.2, 20.3, 19.6, 15.3, 15.2, 14.6, 11.7. **IR**: 3721(w), 2951(m), 2825(w), 1733(s), 1672(s), 1611(m), 1514(m) cm^{-1}. **HRMS(ESI)** M/Z+ Calc. 288.1362, Obs. 288.1367.



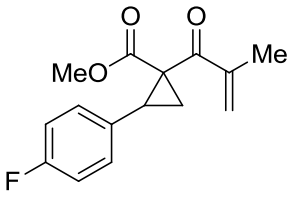
Methyl 1-(cyclohex-1-enecarbonyl)-2-(4-methoxyphenyl)cyclopropanecarboxylate (II-33b). Method B was followed using *t*-BuLi (2.24 mmol, 1.7 M in pentane, 2.0 equiv.), 1-bromocyclohexene (0.400 g, 2.48 mmol, 2.2 equiv.) and Weinreb amide **II-36a** (0.331 g, 1.12 mmol, 1.0 equiv.). Purification by column chromatography (1:9 EtOAc:Hex) afforded **II-33b** (0.159 g, 45% yield) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.18-7.14 (d, 2H, *J* = 12Hz), 6.82-6.72 (d, 2H, *J* =12Hz), 3.76 (s, 3H), 3.38 (s, 3H), 3.34-3.24 (t, 1H, *J* = 12Hz), 2.42-2.30 (m, 1H), 2.26-2.18 (m, 4H), 1.72-1.62 (m, 4H), 1.50-1.44 (m, 1H). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 195.4, 169.4, 158.5, 139.9, 138.8, 129.9, 126.9, 113.4, 55.1, 52.1, 41.4, 29.3, 25.9, 23.6, 21.8, 21.5, 19.5. **IR**: 2956(m), 2872(w), 1731(s) cm^{-1}. **HRMS(ESI)** M/Z+ Calc. 314.1518, Obs. 384.1524.



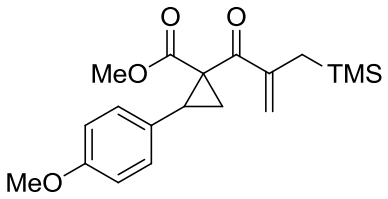
Methyl 1-methacryloyl-2-(4-methoxyphenyl)cyclopropanecarboxylate (II-33c). Method A was followed using prop-1-en-2-ylmagesium bromide (2.65 mL, 1.32 mmol, 0.5M in THF, 1.3 equiv.) and amide **II-36a** (0.300 g, 1.02 mmol, 1.0 equiv.). The reaction was quenched after 2 h to give **II-33c** (0.196 g, 70% yield) after purification via flash chromatography (1:6 EtOAc/Hex) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.18-7.10 (d, 2H, *J* = 12Hz), 6.80-6.74 (d, 2H, *J* = 12Hz), 5.88 (s, 1H), 5.60 (s, 1H), 3.76 (s, 3H), 3.34(s, 3H), 2.30-2.22 (m, 1H), 1.94 (s, 3H), 1.52-1.46 (m, 1H). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 196.5, 169.1, 158.6, 144.4, 129.9, 128.7, 126.7, 123.7, 113.6, 113.4, 55.1, 52.1, 41.7, 29.8, 20.1, 17.9. **IR**: 2951(m), 2837(m), 1734(s), 1673(s), 1558(s), 1515(s) cm^{-1}. **HRMS(ESI)** M/Z+ Calc. 274.1305, Obs. 274.1305.



Methyl 1-methacryloyl-2-phenylcyclopropanecarboxylate (II-33d). Method A was followed using prop-1-en-2-ylmagesium bromide (8.69 mL, 4.34 mmol, 0.5M in THF, 2.2 equiv.) and amide **II-36b** (0.520 g, 1.97 mmol, 1.0 equiv.). The reaction was quenched after 2.5 h to give **II-33d** (231.3 mg, 48% yield) after purification via flash chromatography (1:6 EtOAc/Hex) as colorless oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.30 (m, 5H), 5.90 (s, 1H), 5.70 (s, 1H), 3.42-3.36 (t, 1H, *J* = 9Hz, 9Hz), 2.36-2.28 (dd, 1H, *J* = 3 Hz, 6 Hz), 1.94 (s, 3H), 1.74-1.68 (dd, 1H, *J* = 3Hz, 6 Hz). **^{13}C NMR** ($CDCl_3$, 75 Hz) δ 190.1, 168.8, 144.2, 134.8, 128.8, 127.9, 127.0, 123.7, 52.0, 41.7, 30.1, 19.7, 17.9. **IR**: 3674(m), 2945(m), 2923(w), 2850(w), 1743(m), 1715(s), 1687(m), 1678(m) cm^{-1}. **HRMS(ESI)** M/Z+ Calc. 244.1099, Obs. 244.1101.

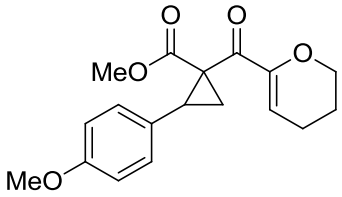


Methyl 2-(4-fluorophenyl)-1-methacryloylcyclopropanecarboxylate (II-33e). Method A was followed using prop-1-en-2-ylmagesium bromide (6.3 mL, 3.128 mmol, 0.5M in THF, 2.2 equiv.) and amide **II-36c** (0.400 g, 1.42 mmol, 1.0 equiv.). The reaction was quenched after 3 h to give **II-33e** (0.149 mg, 40% yield) after purification via flash chromatography (1:6 EtOAc/Hex) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.22-7.16 (d, 2H, *J* = 18Hz), 6.98-6.90 (d, 2H, *J* = 18Hz), 5.90 (s, 1H), 5.70 (s, 1H), 3.36 (s, 3H), 3.36-3.30 (t, 1H, *J* = 12Hz, 6Hz), 2.28-2.22 (m, 1H), 1.94 (s, 3H), 1.56-1.44 (m, 1H). **^{13}C NMR** ($CDCl_3$, 75 Hz) δ 195.9, 168.7, 136.5, 160.3, 144.2, 130.5, 130.2, 115.1, 114.7, 52.1, 41.6, 29.3, 21.6, 19.9, 17.8. **IR**: 2953(m), 1740(s), 1678(s), 1509(s), 1435(w) cm^{-1}. **HRMS(ESI)** M/Z+ Calc. 262.1005, Obs. 262.0996.

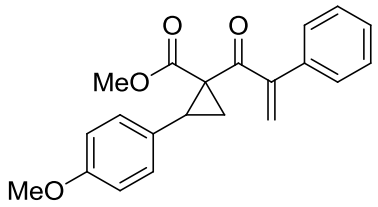


Methyl 2-(4-methoxyphenyl)-1-(2 ((trimethylsilyl)methyl)acryloyl) cyclopropane carboxylate(II-33f). A pre-cooled (-78^{o}C) solution of 2-bromoallyltrimethylsilane (296 mg, 1.53 mmol, 1.5 equiv.) in a solvent mixture of Et_2O (5 mL) and THF (0.25 mL) was treated with *t*-BuLi (1.7 M in pentane, 1.80 mL, 3.0 equiv.) dropwise over 10 min. The light yellow reaction mixture was stirred at -78^{o}C for 30 min. A solution of amide **II-36a** (300 mg, 1.02 mmol, 1.0 equiv.) was added dropwise over 10 min. The resulting mixture was stirred at -78^{o}C for another 1 h and warmed up to room temperature. The reaction

was quenched after 1 hr with saturated solution of NH_4Cl. After a usual workup and purification by column chromatography (1:10 EtOAc:Hex) afforded **II-33f** (0.128 g, 36% yield) as a yellowish oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.18-7.08 (d, 2H, *J* = 12Hz), 6.80-6.74 (d, 2H, *J* = 16Hz), 5.82(s, 1H), 5.52(s, 1H), 3.70(s, 3H), 3.30(s, 3H), 3.35-3.25 (t, 1H, *J* = 15Hz), 2.30-2.20 (m, 1H), 2.10 (s, 1H), 1.70 (s, 1H), 1.50-1.30 (m, 1H), 0.00 (s, 9H). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 195.5, 169.1, 158.6, 150.4, 146.4, 129.9, 126.8, 121.4, 113.4, 108.6, 55.0, 51.9, 41.5, 30.1, 26.3, 21.8, 20.6. **IR**: 2951(m), 1735(s), 1673 (s), 1612 (m), 1515 (s) cm^{-1}. **HRMS(ESI)** M/Z+ Calc. 346.1600, Obs. 346.1629.



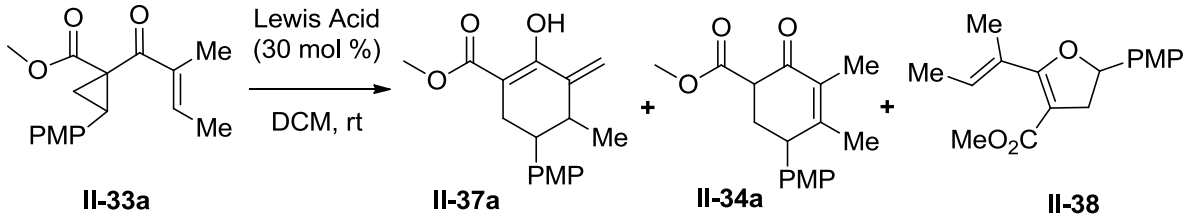
Methyl1-(3,4-dihydro-2H-pyran-6-carbonyl)-2-(4-methoxyphenyl) cyclopropane carboxylate(II-33g). Method B was followed using dihydropyan (0.25 mL, 2.81 mmol, 2.2 equiv.) and amide **II-36a** (0.375 g, 1.28 mmol, 1.0 equiv.). The deprotonation time was 30 min at 0^{o}C and the reaction was quenched after 2 h to give **II-33g** (0.222 g, 55% yield) after purification via flash chromatography (1:9 EtOAc/Hex) as a pale yellow oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.15-7.09 (d, 2H, *J* = 12Hz), 6.80-6.75(d, 2H, *J* = 15Hz), 6.0-5.95 (t, 1H, *J* = 6 Hz, 9Hz), 4.15-4.05 (m, 1H), 4.0-3.9 (m, 1H), 3.75 (s, 3H), 3.40 (s, 3H), 3.36-3.30 (t, 1H, *J* = 6Hz, 6Hz), 2.22-2.18 (m, 3H), 1.90-1.75 (m, 2H), 1.5-1.4 (dd, 1H, *J* = 3.9 Hz, 4.48 Hz, 4.8 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 190.7, 168.4, 158.6, 150.6, 129.9, 126.8, 113.4, 109.9, 66.3, 55.1, 51. 9, 41.2, 29.9, 21.7, 20.6. **IR**: 3622(m), 2951(br, m), 1737(s), 1726(m), 1665(w), 1611(m), 1540(s) cm^{-1}. **HRMS(ESI)** M/Z+ Calc. 316.1311, Obs. 316.1310.



Methyl 2-(4-methoxyphenyl)-1-(2-phenylacryloyl)cyclopropanecarboxylate (II-33h). The title compound was prepared following a previously reported procedure,[43] *t*-BuLi (1.7M in pentane, 2.4 mL, 2.4 equiv.) was added dropwise in a solution of (1-bromovinyl)benzene (375 mg, 1.2 equiv.) in Trap-mixture (THF/Et_2O/Pentane 4:1:1, 0.20M) at -120^{o}C bath [ligroin(30-50), isopropanol, acetone (4:1:1)/liquid N_2). The temperature was kept between -120^{o}C and -110^{o}C for 1 hour, and then raised to -90^{o}C. A solution of amide **II-36a** (500 mg, 1.0 equiv.) in THF (0.20M) was added slowly dropwise. The reaction was stirred at -90^{o}C for 30 min. The reaction controlled via TLC. The solution was finally warmed upto room temperature (1 h), quenched with saturate solution of NH_4Cl (5 mL/mmol), and followed up by usual workup. Purification by column chromatography (1:9 EtOAc:Hex) afforded **II-33h** (124 mg, 22% yield) as a white solid. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.42-7.24 (m, 5H), 7.18-7.12 (d, 2H, *J* = 12Hz), 6.82-6.76 (d, 2H, *J* = 12Hz), 5.98 (s, 1H), 5.84 (s, 1H) 3.76 (s, 3H), 3.58-3.40 (m, 1H), 3.24 (s, 3H), 2.38-2.30 (ddd, 1H, *J* = 1.05Hz, 4.64Hz, 8.22 Hz), 1.88-1.70 (dd, 1H, *J* = 5.17Hz , 9.65Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 197.6, 168.4, 158.7, 149.7, 136.6, 129.9, 129.0, 128.4, 128.0, 127.8, 126.5, 124.0, 121.5, 113.7, 83.3, 55.1, 52.0, 43.7, 32.2, 22.2. **IR**: 3721(m), 3630 (m), 2951 (m), 2844(m), 1737 (m), 1729(s), 1687(s), 1678(w), 1646(w), 1635(m) cm^{-1}. **HRMS(ESI)** M/Z+ Calc. 336.1362, Obs. 336.1365.

2.7.2.4. Lewis Acid Screening Method

Alkenyl cyclopropyl ketone **II-33a** (0.36 mmol, 1.0 equiv.) was added to a solution of a Lewis acid (0.30 equiv.) in anhydrous dichloromethane (2 mL) at room temperature. Each reaction was stirred from 1 h up to a maximum time of 105 h. An aliquot of the reaction mixture was concentrated. A crude ^{1}H NMR was taken for each Lewis acid.

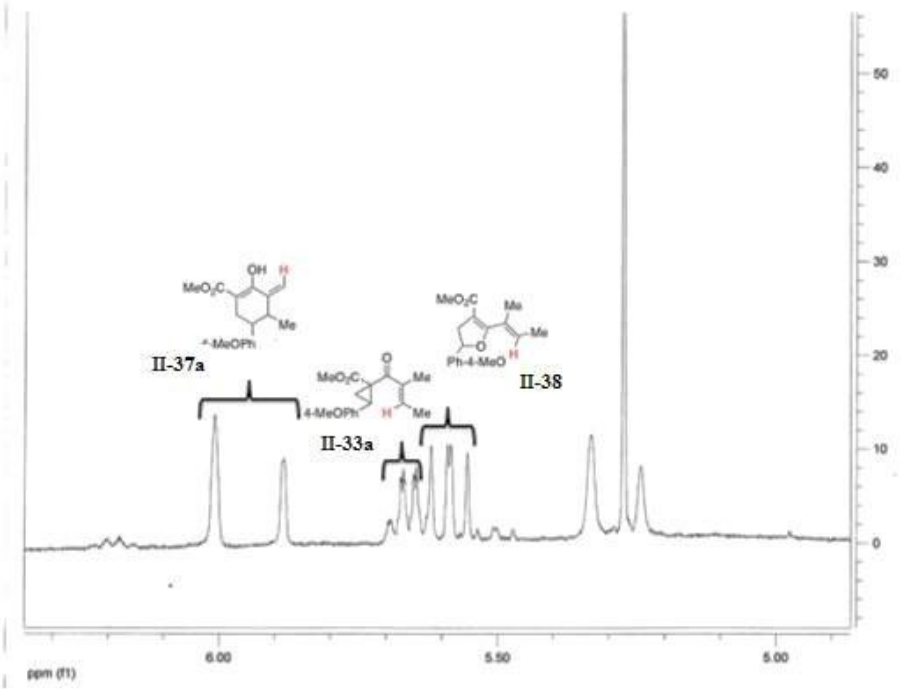


Methyl 2-hydroxy-5-(4-methoxyphenyl)-4-methyl-3-methylenecyclohex-1-enecarboxylate (II-37a). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 12.05 (s, 1H), 7.20-7.10 (d, 2H, *J* = 9Hz), 6.90-6.80 (d, 2H, *J* = 15Hz), 6.02-5.88(d, 1H, *J* = 36Hz), 5.34-5.24 (d, 1H, *J* = 30Hz), 3.82 (s, 3H), 3.78 (s, 3H), 3.76 (s, 3H), 3.72 (s, 3H), 3.10-3.00 (s, 1H), 2.80-2.40 (m, 4H), 1.00 (d, 3H, *J* = 12Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 173.5, 164.1, 163.6, 158.4, 144.7, 143.7, 137.0, 135.2, 128.9, 122.6, 114.2, 113.9, 98.9, 55.2, 52.2, 46.4, 42.1, 41.3, 39.3. **IR**: 2928 (m), 1717(w), 1654(m), 1628(w), 1512(s) cm^{-1}. **HRMS(ESI)** M/Z+ Calc. 288.1362, Obs. 288.1360.

Methyl 5-(4-methoxyphenyl)-3,4-dimethyl-2-oxocyclohex-3-enecarboxylate (II-34a). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.08-7.00 (d, 2H, *J* =6Hz), 6.88-6.81(d, 2H, *J* =10.5Hz), 3.78(s, 3H), 3.68(s, 3H), 3.42-3.36(m, 1H), 2.76-2.64 (m, 1H), 2.38-2.30(m, 1H), 2.10-2.02(m, 1H), 1.90(s, 3H), 1.80(s, 3H). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 193.6, 171.1,

158.7, 156.7, 155.9, 134.9, 132.3, 132.0, 129.2, 128.7, 122.2, 114.3, 114.2, 113.8, 55.3, 55.2, 53.2, 52.2, 52.1, 49.1, 47.3, 45.5, 34.5, 33.7, 20.9, 20.4, 11.6, 11.2. **IR**: 2929(m), 1717(w), 1654(s), 1627(w), 1586(m), 1512(m) cm^{-1}. **HRMS(ESI)** M/Z+ Calc. 288.1362, Obs. 288.1367.

(E)-Methyl 2-(but-2-en-2-yl)-5-(4-methoxyphenyl)-4,5-dihydrofuran-3-carboxylate (II-38). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.30 (d, *J* = 8.39 Hz, 2H), 6.90 (d, *J* = 8.39 Hz, 2H), 5.70-5.56 (m, 1H), 3.81 (s, 3H), 3.80-3.74 (m, H), 3.65(s, 3H), 3.38 (dd, *J* = 14.87, 10.72 Hz, 1H), 3.02 (dd, *J* = 14.88, 8.64 Hz, 1H), 2.01-1.88 (m, 3H), 1.69-1.60 (m, 3H). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 166.6, 165.3, 159.5, 133.5, 128.7, 127.3, 126.9, 114.0, 102.8, 83.2, 55.3, 50.9, 38.1, 21.4, 15.4. **IR**: 3648.6(w), 2947.0(m), 2847.6(m), 1791.45(s), 1709.75(s), 1652.5(m), 1618.4(w), 1576.1(w) cm^{-1}. **HRMS(ESI)** M/Z+ Calc. 288.1362, Obs. 288.1364.



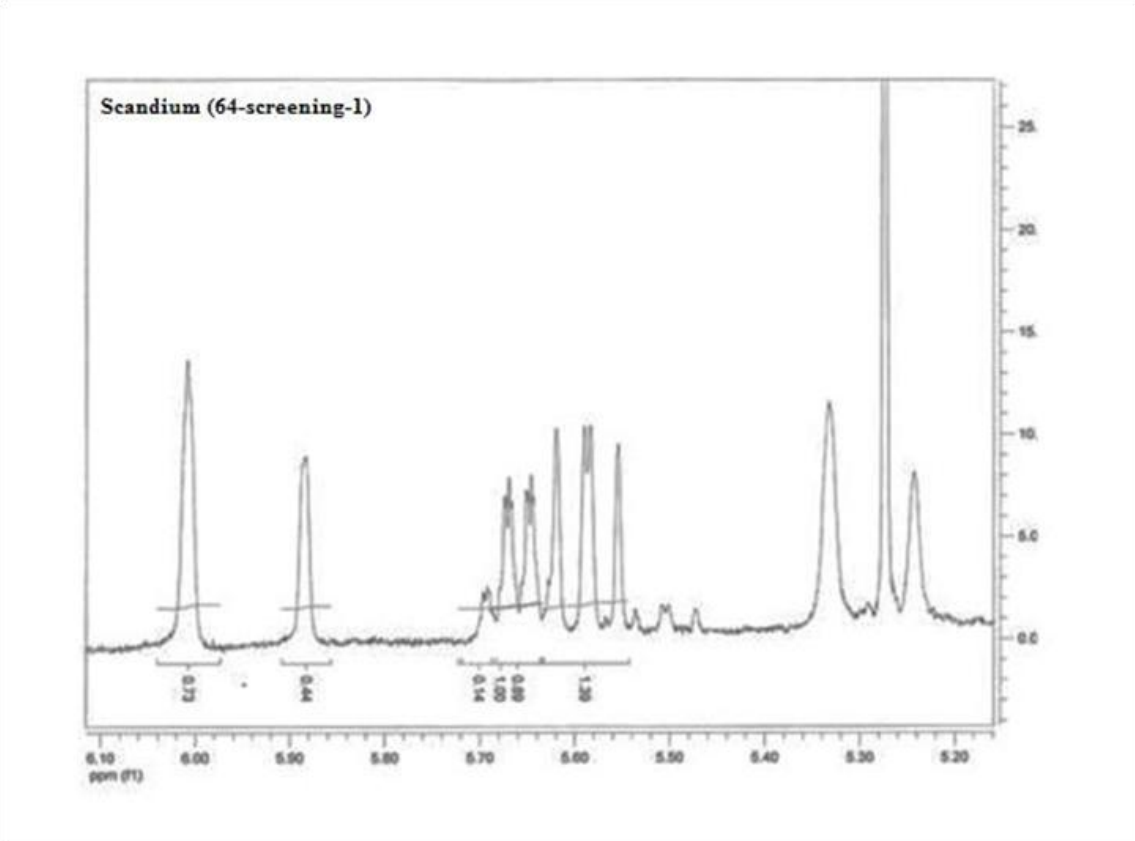


Figure 2.32. Representative Crude NMR Spectra for Lewis Acid Screening

Determination of Product Ratios: The ratios of **II-37a**:**II-34a**:**7II-38**:**II-33a** were determined by examining the 5.0-6.5 ppm region of each NMR spectrum and comparing the relative integrations representing **II-37a**, **II-38** and **II-33a** (Figure 2.32). The amount of **II-34a** was extrapolated based on the 1.5:1 ratio of **II-37a**:**II-34a**, which is determined from isolated yields. The integral value for **II-33a** was set to 1 and the relative integrals for **II-37a**, and **II-38**, as well as the calculated integral for **II-34a**, were subjected to the following calculations:

II-37a + **II-34a** + **II-38** + **II-33a** = Total

% **II-37a**: (**II-37a** /Total)*100

% **II-34a**: (**II-34a** / Total)*100

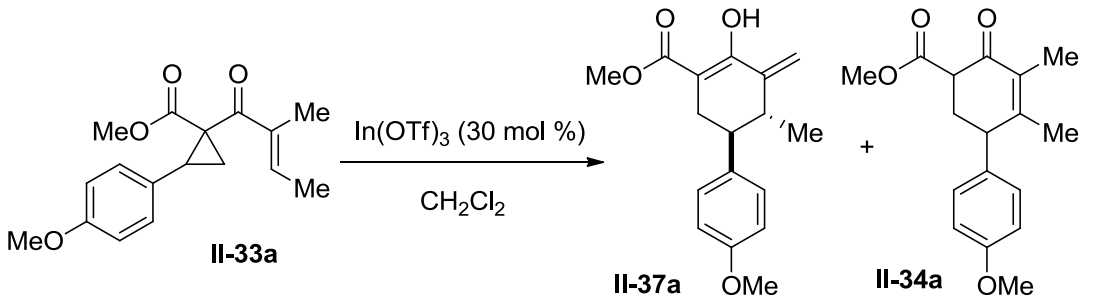
% **II-38**: (**II-38** / Total)*100

% **II-33a**: (**II-33a** / Total)*100

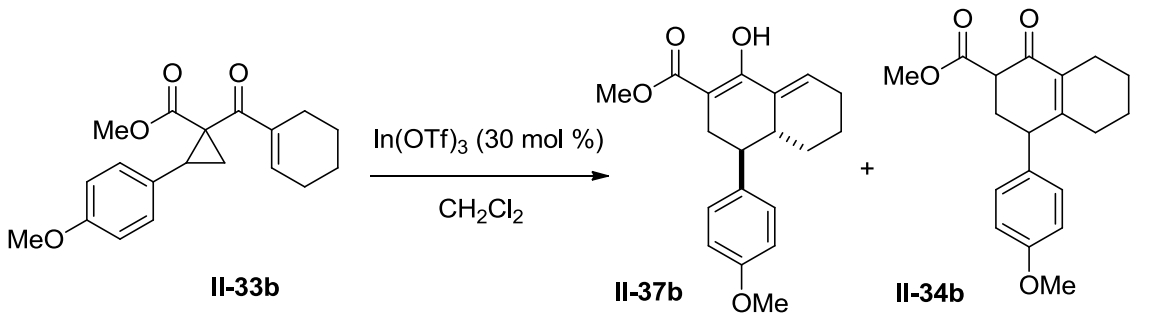
Final ratios are based on: (%**II-37a** +% **II-34a**):% **II-38**:% **II-33a**

2.7.2.5. $In(OTf)_3$-Catalyzed Cyclizations

General Procedure: Alkenyl cyclopropyl ketone (0.36 mmol, 1.0 equiv.) was added to a solution of an $In(OTf)_3$ (41 mg, 72 µmol, 0.30 equiv.) in anhydrous dichloromethane (2 mL) at room temperature. The reaction was stirred during the indicated time. The reaction mixture was quenched with water (5 mL) and extracted with dichloromethane (3x10 mL). The combined organic layers were washed with brine (3x 10 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure.



II-33a (50 mg, 0.19 mmol) was added to a room-temperature solution of $In(OTf)_3$ (30.8 mg, 0.056 mmol, 0.3 equiv.). After 3 hours, reaction was completed, and the standard work-up was performed. Column chromatography afforded products **II-37a** (23.4 mg) and **II-34a** (14 mg) as yellow oil (74.8% yield). R_f (20% EtOAc/Hex): **II-37a**: 0.6; **II-34a**:0.25.



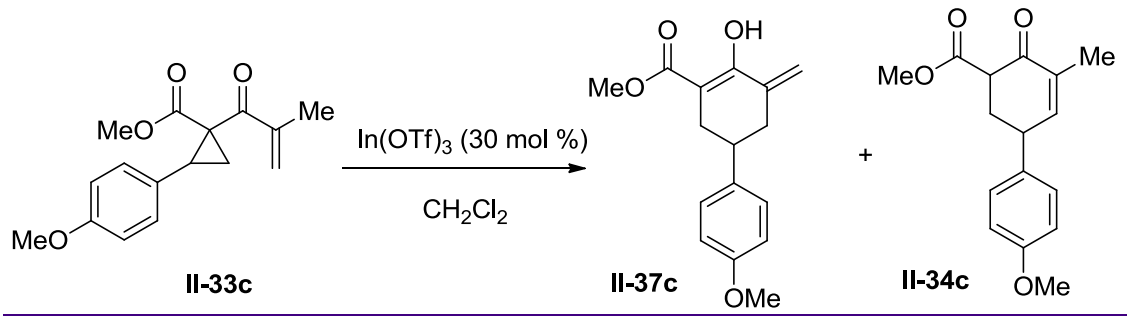
II-33b **II-37b** **II-34b**

II-33b (50 mg, 0.16 mmol) was added to a room-temperature solution of $In(OTf)_3$ (61.5 mg, 0.11 mmol, 0.3 equiv.) at room temperature. After 40 minutes, reaction was completed, and the standard work-up was performed. Column chromatography afforded products **II-37b** (29 mg) and **II-34b** (9.6 mg) as a yellow oils (77% yield). R_f (20% EtOAc/Hex): **II-37b**: 0.6; **II-34b**: 0.2.

Methyl 1-hydroxy-4-(4-methoxyphenyl)-3,4,4a,5,6,7-hexahydronaphthalene-2-carboxylate(II-37b). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.1(s, 1H), 7.15-7.05 (d, 2H, *J* = 15Hz), 6.9-6.8 (d, 2H *J* = 24Hz), 3.8 (s, 3H), 3.7 (s, 3H), 2.7-2.55 (m, 1H), 2.4 (s, 3H), 2.3-2.1 (m, 2H), 1.75-1.65 (m, 1H), 1.5-1.35 (m, 2H), 1.00-0.85 (m, 1H). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 173.2, 163.8, 158.1, 136.1, 132.6, 130.9, 128.4, 113.8, 97.6, 55.2, 51.5, 46.5, 40.0, 31.9, 28.2, 26.1, 21.5. **IR**: 3654(b), 3445(m), 3021(w), 2924(m), 2841(m), 1733(s), 1654(s), 1611(w), 1512(w) cm^{-1}. **HRMS(ESI)** M/Z+ Calc. 314.1518, Obs. 314.1522.

Methyl 4-(4-methoxyphenyl)-1-oxo-1,2,3,4,5,6,7,8-octahydronaphthalene-2 carboxylate (II-34b). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.08-7.00 (d, 2H, *J* = 12Hz), 6.88-6.82 (d, 2H, *J* = 9Hz), 3.78 (s, 3H), 3.7 (s, 3H), 3.5-3.36 (m, 1H), 2.8-2.64 (m, 1H), 2.50-2.30 (m, 3H), 2.18-2.00 (m, 2H), 1.70-1.60 (m, 5H). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 193.6, 171.1, 158.7, 158.6, 157.7, 134.4, 133.4, 132.2, 129.3, 128.9, 128.7, 114.2, 55.3,

53.4, 52.1, 49.4, 46.4, 44.2, 34.4, 30.7, 30.5, 22.8. **IR**: 2929(s), 2854 (m), 1740 (s), 1666 (s), 1632(m), 1610(m) cm^{-1}. **HRMS(ESI)** M/Z+ Calc. 314.1518, Obs. 384.1518.



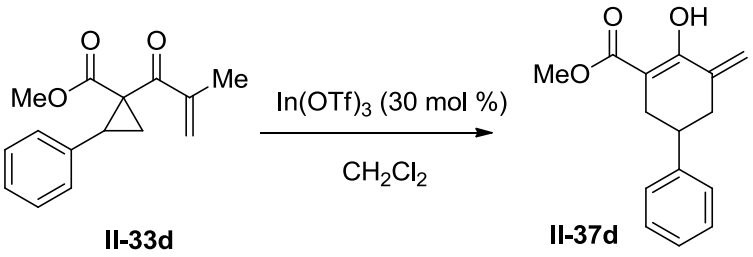
II-33c **II-37c** **II-34c**

II-33c (100 mg, 0.36 mmol) was added to a room-temperature solution of $In(OTf)_3$ (61.5 mg, 0.11mmol, 0.3 equiv.). After 40 minutes, reaction was completed, and the standard work-up was performed. Column chromatography afforded products **II-37c** (45 mg) and **II-34c** (10 mg) as a yellow oils (75.6% yield). R_f (20% EtOAc/Hex): **II-37c:** 0.6; **II-34c**: 0.2.

Methyl 2-hydroxy-5-(4-methoxyphenyl)-3-methylenecyclohex-1-enecarboxylate (II-37c). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.00 (s, 1H), 7.20-7.15 (d, 2H, *J* = 12 Hz), 6.90-6.80 (d, 2H, *J* =15 Hz), 5.85 (s, 1H), 5.20 (s, 1H), 3.80 (s, 3H), 3.65 (s, 3H), 2.85-2.80 (m, 1H), 2.75-2.45 (m, 3H), 2.40-2.30 (m, 1H). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 173.1, 163.8, 158.2, 138.5, 136.9, 127.6, 116.5, 113.9, 99.6, 55.3, 51.7, 39.3, 38.2, 31.7. **IR**: 3733 (m), 2951(m), 2850 (w), 1654, 1631, 1582 cm^{-1}. **HRMS(ESI)** M/Z+ Calc. 274.1205, Obs. 274.1214.

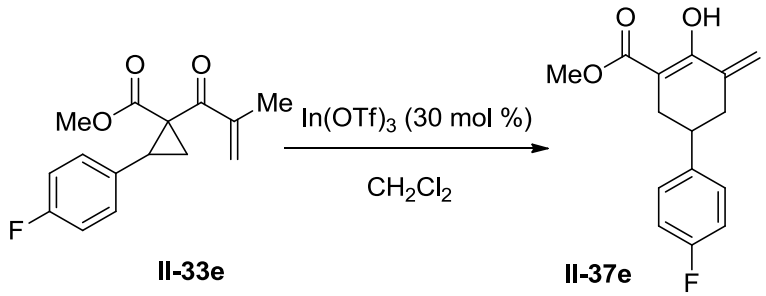
Methyl 5-(4-methoxyphenyl)-3-methyl-2-oxocyclohex-3-enecarboxylate (II-34c). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.15-.7.08 (d, 2H, *J* = 12Hz), 6.80-6.72 (d, 2H, *J* = 9Hz), 3.78 (s, 3H), 3.74 (s, 3H), 3.54-3.46 (m, 1H), 2.74- 2.62 (m, 1H), 2.42-2.36 (m, 1H), 2.20-2.10 (m, 1H), 1.85 (s, 3H). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 194.4, 170.0, 158.6,

149.2, 148.0, 135.4, 133.9, 128.7, 122.2, 115.9, 114.7, 113.8, 55.3, 41.7, 39.2, 35.8, 16.2. **IR**: 2953, 2831, 1740, 1676, 1635, 1540 cm^{-1}. **HRMS(ESI)** M/Z+ Calc. 274.1205, Obs. 274.1204.



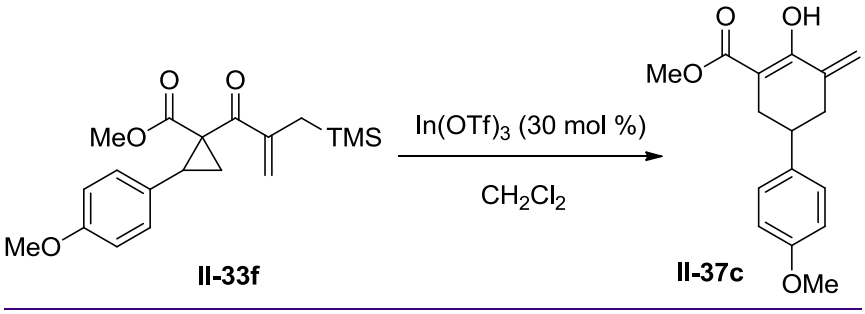
II-33d **II-37d**

Methyl 2-hydroxy-3-methylene-5-phenylcyclohex-1-enecarboxylate (II-37d). II-33d (70 mg, 0.28 mmol) was added to solution of indium triflate(48.3 mg, 0.09 mmol, 0.3 equiv.) at room temperature. After 30 hours, reaction was quenched, and the standard work-up was performed. Column chromatography afforded products **II-37d** (32 mg) (45.7% yield). R_f 0.6 (20% EtOAc/Hex) **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.40-7.20(m, 5H), 5.90 (s, 1H), 5.40 (s, 1H), 3.75 (s, 3H), 2.90-2.80 (m, 1H), 2.70-2.60 (m, 3H), 2.40-2.30 (m, 1H). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 173.0, 163.7, 144.7, 138.4, 128.5, 126.7, 126.5, 122.2, 116.6, 99.6, 51.8, 40.1, 37.9, 31.5, 14.5. **IR**: 3026(w), 2922(m), 2850(w), 1654(s), 1631(m), 1438(s) cm^{-1}. **HRMS(ESI)** M/Z+ Calc. 244.1099, Obs. 244.1105.

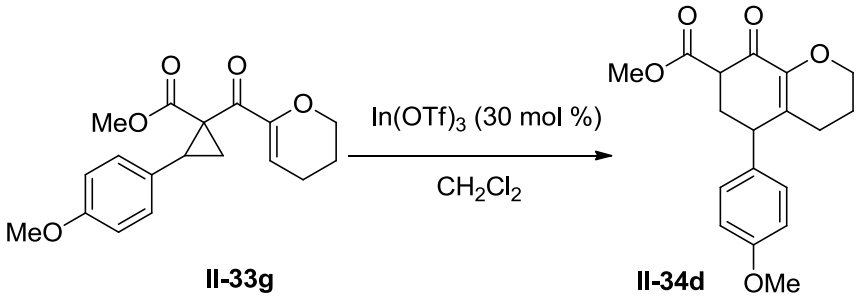


II-33e **II-37e**

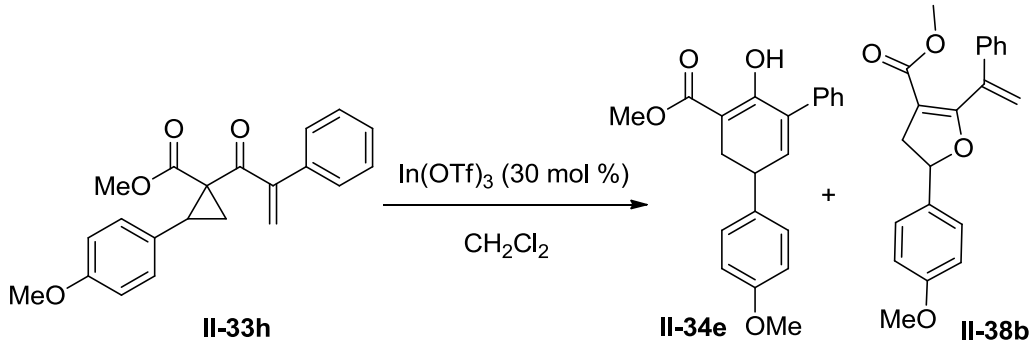
Methyl 5-(4-fluorophenyl)-2-hydroxy-3-methylenecyclohex-1-enecarboxylate (II-37e). II-33e (55 mg, 0.21 mmol) was added to solution of indium triflate(35.3 mg, 0.06 mmol, 0.3 equiv.) at room temperature. After 30 hours, reaction was quenched, and the standard work-up was performed. Column chromatography afforded products **II-37e** (30 mg) (54.5% yield). R_f 0.6 (20% EtOAc/Hex) **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.20-7.10 (d, 2H, *J* =15Hz), 7.00-6.90 (d, 2H, *J* = 12Hz), 5.9 (s, 1H), 5.2 (s, 1H), 3.75 (s, 3H), 2.8-2.7 (m, 1H), 2.70-2.50 (m, 3H), 2.4-2.3 (m, 1H). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 172.9, 163.7, 163.1, 159.8, 140.4, 138.1, 128.1, 116.8, 115.3, 99.4, 51.8, 39.4, 38.1, 31.6. **IR**: 2950(m), 2854(w), 1654(m), 1634(m), 1585(m), 1509(s), 1440(m) cm^{-1}. **HRMS(ESI)** M/Z+ Calc. 262.1005, Obs. 262.1014.



II-33f (50 mg, 0.14 mmol) was added to solution of indium triflate (24.33 mg, 0.043 mmol, 0.3 equiv.) at room temperature. After 20 minutes, reaction was completed, and the standard work-up was performed. Column chromatography afforded product **II-37c** (36.4 mg, 92%) as a yellow oil. R_f (20% EtOAc/Hex): 0.6.



Methyl 5-(4-methoxyphenyl)-8-oxo-3,4,5,6,7,8-hexahydro-2H-chromene-7-carboxylate (II-34d). II-33g (90 mg, 0.28 mmol) was added to solution of indium triflate (31.9 mg, 0.09 mmol, 0.3 equiv.) at 0^{o}C. After 30 min, reaction was completed, and the standard work-up was performed. Column chromatography afforded products **II-34d** (27.8 mg) (92.6% yield). R_f (25% EtOAc/Hex) = 0.2. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.12-7.04 (d, 2H, *J* = 12Hz), 6.84-6.82 (d, 2H, *J* = 12Hz), 4.10-4.06 (t,1H, *J* = 12Hz, 6Hz), 3.72 (s, 3H), 3.70 (s, 3H), 3.60-3.42 (m, 2H), 2.74-2.62 (m, 1H), 2.42-2.28 (m, 1H), 2.18-2.08 (m, 1H), 2.04-1.96 (m, 1H), 1.90-1.75 (m, 3H). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 187.6, 170.1, 158.7, 146.0, 133.7, 132.9, 132.5, 129.2, 128.9, 114.3, 66.0, 55.3, 53.3, 52.4, 50.1, 44.7, 42.8, 34.2, 25.1, 21.8. **IR**: 2952 (m), 1738(s), 1681(s), 1610(s), 1582(w) cm^{-1}. **HRMS(ESI)** M/Z+ Calc. 316.1311, Obs. 316.1303.



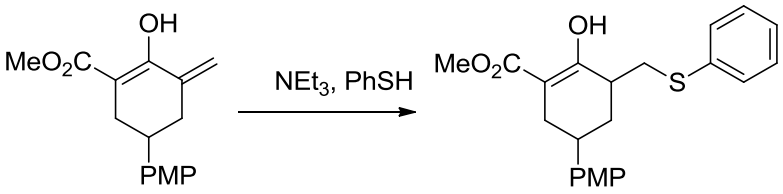
II-33h (23 mg, 0.07 mmol) was added to solution of indium triflate (11.54 mg, 0.02 mmol, 0.3 equiv.) at room temperature. After 12 hours, the reaction was stopped, and the

standard work-up was performed. Column chromatography afforded the desired product **II-34e** (6.67 mg, 29% yield) as the minor component (R_f 0.6 (20% EtOAc/Hex). **II-38b** (9.4 mg, 41%) was isolated as the major component. Starting material **II-33h** (7 mg) was also recovered from the reaction mixture.

Methyl 2-hydroxy-5-(4-methoxyphenyl)-3-phenylcyclohexa-1,3-dienecarboxylate (II-34e). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.2 (s, 1H), 7.4-7.2(m, 6H), 7.2-7.1 (d, 2H, *J* = 12Hz), 6.9-6.8 (d, 2H, *J* = 9Hz), 3.85 (s, 1H), 3.75 (s, 1H), 3.23-3.1 (t, 1H, *J* = 9Hz, 12Hz), 2.9 (s,1H), 2.8-2.7 (m, 1H), 2.4-2.2 (m, 2H), 2.08-1.96 (m, 1H). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 172.9, 169.8, 158.1, 145.2, 136.6, 128.3, 127.4, 124.9, 114.4, 113.8, 100.7, 55.3, 51.9, 47.4, 35.9, 31.7. **IR**: 2952(m), 2836(w), 1723(s), 1678(s), 1610(m), 1510(m) cm^{-1}. **HRMS(ESI)** M/Z+ Calc. 336.1362, Obs. 336.1361.

Methyl 5-(4-methoxyphenyl)-2-(1-phenylvinyl)-4,5-dihydrofuran-3-carboxylate (II-38b). R_f 0.45 (20% EtOAc/Hex). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.57 (d, *J* = 8.11 Hz, 2H), 7.45-7.28 (m, 5H), 6.92 (d, *J* = 8.2 Hz, 2H), 5.72-5.61 (m, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.42 (dt, *J* = 8.11, 8.11, 8.11 Hz, 1H), 3.07 (t, *J* = 8.93Hz, 16.18 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 164.8, 159.8, 147.0, 132.6, 132.2, 128.4, 127.5, 126.3, 114.1, 114.0, 111.4, 98.2, 84.1, 79.3, 55.3, 51.4, 37.7. **IR**: 2950.4(w), 2924.9(m), 2851.3(m), 1689.8(s), 1614.0(s), 1514.4(m), 1439.0(m) cm^{-1}. **HRMS(ESI)** M/Z+ Calc. 336.1362, Obs. 336.1370.

2.7.2.6. Derivatization of Products



II-37c **II-39**

Methyl 2-hydroxy-5-(4-methoxyphenyl)-3-(phenylthiomethyl)cyclohex-1-enecarboxylate (II-39). Et_3N (13.9 µL, 1.1 equiv.) was added dropwise at room temperature to a stirred solution of **II-37c** (25 mg, 0.09 mmol, 1.0 equiv.) and thiophenol (14 µL, 1.5 equiv.) in $CHCl_3$ (1 mL). After 14 h, the reaction mixture was directly purified by flash chromatography using 1:11 EtOAc:Hex) to give the thioether **II-39** (20.3 mg, 58% yield). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 12.04(s, 1H), 7.40-7.10 (m, 7H), 6.90-6.80 (d, 2H, *J* =12Hz), 3.80 (s, 1H), 3.70 (s, 3H), 3.0-2.90 (m, 2H), 2.70-2.60 (m, 2H), 2.35-2.20 (m, 2H), 1.90-1.78 (m, 1H). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 172.8, 171.6, 158.1, 137.1, 129.01, 127.7, 127.6, 126.04, 113.8, 98.3, 55.3, 51.6, 38.3, 35.7, 34.4, 31.6, 30.8. **IR**: 3625(w), 2926(m), 2850(w), 1716(m), 1654(s), 1611(m), 1512(s) 1438(s) cm^{-1}. **HRMS(ESI)** M/Z+ Calc. 384.1395, Obs. 384.1401.

II-34a **II-40**

4-(4-Methoxyphenyl)-2,3-dimethylcyclohex-2-enone (II-40). A 10 mL flask open to air was charged with diester **II-34a** (50 mg, 0.17 mmol), NaCl (10.63 mg, 0.182 mmol), water (6.25 μL, 0.346 mmol) and DMSO (2 mL) at room temperature. The flask was fitted with a reflux condenser and heated to 150˚C with vigorous stirring. After heating for 12 h TLC analysis indicated consumption of starting material, and the reaction was cooled to 22˚C. The reaction was diluted with 7:3 hexane/Et_2O (25 mL) and washed with water (3x 5 mL). The organic layer was dried over $MgSO_4$, concentrated, and purified by silica gel chromatography (2:3 EtOAc/Hex) to afford **II-40** (30 mg, 74% yield). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.10-7.00 (d, 2H, *J* = 12Hz), 6.86-6.82 (d, 2H, *J* =12Hz), 3.78 (s), 3.60-3.50 (s, 1H), 2.40-2.24 (m, 3H), 1.84 (s, 3H), 1.76 (s, 3H). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 198.8, 158.6, 155.4, 133.5, 130.6, 129.2, 114.2, 55.3, 47.2, 33.9, 31.1, 20.6, 17.45. **IR:** 2925(m), 2835(w), 1661(s), 1609(w), 1509(s), 1453(w) cm^{-1}. **HRMS(ESI)** M/Z+ Calc. 230.1307, Obs. 230.1313.

2.8. EXPERIMENTAL SECTION FOR FORMAL HOMO-NAZAROV CYCLIZATION OF HETEROARYL CYCLOPROPYL KETONES

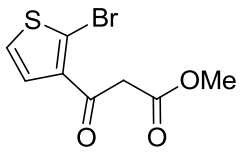
2.8.1. General Methods

Infrared (IR) spectra were obtained using a Nicolet 4700 FTIR with an ATR attachment from SmartOrbit Thermoelectronic Corp. Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Varian Mercury Vx 300 spectrometer with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, ddd = doublet of doublet of doublets, ddt = doublet of doublet of triplets, dtd = doublet of triplet of doublets, t = triplet, bt = broad triplet, td = triplet of doublets, q = quartet, qd = quartet of doublets, qn = quintet, m = multiplet), coupling constants (Hz), and integration. Mass spectra were obtained using a VG-70SE instrument. Chromatographic purification was performed as flash chromatography using Dynamic Adsorbents silica gel (32-65μm), using the solvents indicated as eluent with 0.1-0.5 bar pressure. For quantitative flash chromatography technical grades solvents were used. Analytical thin-layer chromatography (TLC) was performed on EMD silica gel 60 F_{254} TLC glass plates. Visualization was accomplished with UV light, aqueous basic potassium permanganate ($KMnO_4$) solution, iodine, aqueous acidic dinitrophenylhydrazine (DNP) solution, aqueous acidic *p*-anisaldehyde (PAA) solution, and ethanol solution of phosphomolybdic acid (PMA) followed by heating. Yields refer to isolated yields of analytically pure material unless otherwise

noted. All reactions were carried out in oven-dried glassware under an atmosphere of N_2, unless stated otherwise. Tetrahydrofuran and diethyl ether were distilled from a sodium/benzophenone ketyl under N_2 and stored in a Schlenk flask. 1,2-dichloroethane and dichloromethane was purified by distillation from calcium hydride under N_2 prior to use. Acetonitrile was dried by fractional distillation over CaH_2. Benzene was purified by drying with CaH_2. Lithium bis(trimethylsilyl)amide (LHMDS) was purchased from Sigma-Aldrich as a 1.0 M solution in THF. *n*-Butyllithium was purchased from Sigma-Aldrich as a 2.5 M solution in hexanes. *t*-Butyllithium was purchased from Sigma-Aldrich as a 1.7 M solution in hexanes. Nitromethane was distilled over CaH_2 and stored under nitrogen under 4Å molecular sieves. All other reagents were purchased from Acros, Sigma-Aldrich, Fluka, VWR, Merck, Alfa Aesar, TCI and Strem (for metal catalysts) and used without further purification unless otherwise noted. Compounds **II-50a, II-50b, II-50c, II-50e, II-50f, II-50g** were made via a modified Warner's method.[44] Compound **II-50d** was prepared by a modified version of Frontier's method.[37] Compound **II-50h** was prepared based on Kanda's protocol.[45]

2.8.2. General Procedures

2.8.2.1. Formation of β-Keto ester II-50i

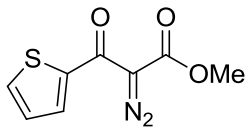


Methyl 3-(2-bromothiophen-3-yl)-3-oxopropanoate(II-50i). 2-Bromo-3-thiophene carboxylic acid chloride was prepared from a solution of 2-bromo-3-thiophene carboxylic acid (0.50 g, 2.41 mmol) in DCM(0.5M) and was added a catalytic amount of *N*,*N*'-

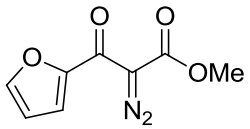
dimethylformamide (0.2 mL). The solution was cooled to 0°C, and to it was added oxallyl chloride (0.25 mL 2.9 mmol). LHMDS (5.1mL, 5.1 mmol) was added to a solution of methyl acetate (0.21 mL, 2.54 mmol) in THF at -78°C and allowed to stir for 45 minutes. To the solution of the enolate was added the 2-bromo-3-thiophene acid chloride in 10 mL of THF. Reaction was allowed to stir for 30 minutes at -78°C, quenched with saturated ammonium chloride. Reaction was then allowed to warm up to rt, extracted with Et_2O, washed with brine, and dried with anhydrous Na_2SO_4. The solution was then concentrated and column chromatography (15% EtOAc/Hex, R_f 0.3) afforded **II-50i** as an oil (0.317g, 50.4%). (4:1 mixture of ester and enol) **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 12.4 (s, 0.23, enol) 7.34 (d, *J* = 5.85 Hz, 1H), 7.24 (d, *J* = 5.84 Hz, 1H), (5.80, s, 0.23, enol), 4.01-3.96 (s, 2H), 3.76-3.69 (s, 3H); **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 186.489, 167.498, 128.921, 126.578, 119.415, 90.181, 52.485, 51.554. IR: 3103(w), 2940(w), 2021(m), 1957(m), 1731(m), 1658(m), 1512(w), 1402(w), 1309(m), 1213(m) cm $^{-1}$. HRMS(ESI) M/Z+ Calc. 261.9299, Obs. 261.9299.

2.8.2.2. General procedure for the formation of α-diazo-esters (II-51a-m)

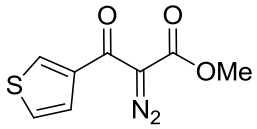
In a flame dried flask containing a solution of the β-keto ester in acetonitrile (0.2 M) was added Et_3N (1.2 equiv.). After vigorous stirring for 5 minutes, tosyl azide (1.2 equiv.) was added, and the reaction was allowed to stir for 3 hrs. After complete disappearance of starting material, mixture was concentrated *in vacuo*, followed by column chromatography to furnish the desired diazo compound.[40]



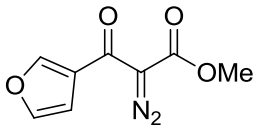
Methyl 2-diazo-3-oxo-3-(thiophen-2-yl)propanoate (II-51a). According to the general procedure, to a solution of the β-keto ester **II-50a** (1.50 g, 8.14 mmol) in acetonitrile was added Et_3N (1.4 mL, 9.77 mmol) and tosyl azide (1.93 g, 9.77 mmol). Column chromatography (10% EtOAc/Hex, R_f 0.25) furnished compound **II-51a** as a yellow oil (1.20 g, 69.5%). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 8.06 (dd, *J* = 3.91, 1.12 Hz, 1H), 7.66 (dd, *J* = 4.99, 1.12 Hz, 1H), 7.12 (dd, *J* = 4.98, 3.92 Hz, 1H), 3.92-3.82 (s, 3H) ppm; **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 176.3, 161.1, 141.2, 133.8, 127.6, 52.2. **IR**: 3100(m), 2947(m), 2146(s, N_2 stretch), 1721(s), 1712(s), 1692(s), 1617(s), 1604(s), 1433(m), 1299(s) cm $^{-1}$. **HRMS(ESI)** M/Z+ Calc. 210.0099, Obs. 210.0095.



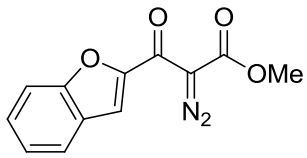
Methyl 2-diazo-3-(furan-2-yl)-3-oxopropanoate (II-51b). According to the general procedure, to a solution of the β-keto ester **II-50b** (0.75 g, 4.46 mmol) in acetonitrile was added Et_3N (0.75 mL, 5.35 mmol) and tosyl azide (1.06 g, 5.35 mmol). Column chromatography (10% EtOAc/Hex, R_f 0.20) furnished **II-51b** as a bright yellow oil (0.614 g, 71.0%). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.62-7.44 (m, 1H), 7.28-7.20 (m, 1H), 6.72-6.19 (m, 1H), 3.90-3.82 (s, 3H); **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 170.7, 161.5, 150.4, 146.0, 145.9, 119.4, 112.3, 52.5. **IR**: 3102(w), 2953(w), 2140(s,N_2), 1717(s), 1584(s), 1514(m), 1434(m), 1410(w) cm^{-1}. **HRMS(ESI)** M/Z+ Calc. 194.0328, Obs. 194.0323.



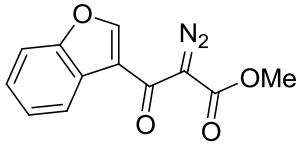
Methyl 2-diazo-3-oxo-3-(thiophen-3-yl)propanoate (II-51c). According to the general procedure, to a solution of the β-keto ester **II-50c** (1.50 g, 8.14 mmol) in acetonitrile was added Et_3N (1.4 mL, 9.77 mmol) and tosyl azide (1.93 g, 9.77 mmol). Column chromatography (10% EtOAc/Hex, R_f 0.20) furnished **II-51c** as a yellow oil (1.10 g, 64.7%). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 8.17 (dd, *J* = 2.95, 1.26 Hz, 1H), 7.47 (dd, *J* = 5.12, 1.15 Hz, 1H), 7.26 (dd, *J* = 5.11, 2.96 Hz, 1H), 3.84-3.77 (s, 3H). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 179.0, 161.4, 138.9, 132.9, 127.9, 124.9, 52.3. **IR**: 3102 (w), 2943(w), 2126 (br s, N_2 stretch), 1721(s), 1212(s), 1604(m), 1498(m), 1435(m), 1299(s) cm $^{-1}$. **HRMS(ESI)** M/Z+ Calc. 210.0101, Obs. 210.0106.



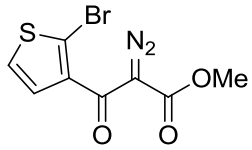
Methyl 2-diazo-3-(furan-3-yl)-3-oxopropanoate (II-51d). According to the general procedure, to a solution of the β-keto ester **II-50d** (1.50 g, 8.9 mmol) in acetonitrile was added Et_3N (1.5 mL, 10.7 mmol) and tosyl azide (2.1 g, 10.7 mmol). Column chromatography (10% EtOAc/Hex, R_f 0.20) furnished **II-51d** as a bright yellow oil (1.17 g, 68.0%). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 8.45-8.35 (m, 1H), 7.52-7.28 (m, 1H), 6.88-6.81 (m, 1H), 3.89-3.76 (s, 3H); **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 177.5, 161.2, 148.9, 142.7, 124.9, 110.2, 52.2. **IR**: 3143(w), 2957(w), 2133(s, N_2 stretch), 1721(s), 1711(s), 1604(s), 1509(m), 1369(m), 1323(s), 1284(s), 1178(m), 1119(s) cm $^{-1}$. **HRMS(ESI)** M/Z+ Calc. 194.0328, Obs. 194.0323.



Methyl 3-(benzofuran-2-yl)-2-diazo-3-oxopropanoate (II-51f). According to the general procedure, to a solution of the β-keto ester **II-50f** (0.76 g, 3.50 mmol) in acetonitrile was added Et_3N (0.60 mL, 4.22 mmol) and tosyl azide (0.81 g, 4.22 mmol). Column chromatography (10% EtOAc/Hex, R_f 0.20) furnished **II-51f** as a bright yellow oil (0.48 g, 57.0%). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.77 (s, 1H), 7.65 (ddd, *J* = 4.15, 2.91, 0.69 Hz, 1H), 7.65-7.45 (m, 2H), 7.42-7.28 (m, 1H), 3.93-3.80 (s, 3H). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 172.1, 161.4, 155.0, 150.5, 128.3, 126.8, 123.9, 123.4, 115.1, 112.2, 52.6. **IR**: 3129(w), 2950(w), 1737(s), 1671(s), 1555(s), 1446(m), 1316(w), 1246(m), 1123(s), 1088(m) cm^{-1}. **HRMS(ESI)** M/Z+ Calc. 244.0484, Obs. 244.0479.



Methyl 3-(benzofuran-3-yl)-2-diazo-3-oxopropanoate (II-51h). According to the general procedure, to a solution of the β-keto ester **1II-50h** (0.26 g, 1.18 mmol) in acetonitrile was added Et_3N (0.2 mL, 1.41 mmol) and tosyl azide (0.28 g, 1.41 mmol). Column chromatography (10% EtOAc/Hex, R_f 0.25) furnished **II-51h** as a bright yellow oil (0.25 g, 86.3%). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 8.80-8.71 (s, 1H), 8.24-8.07 (m, 1H), 7.56-7.44 (m, 1H), 7.38-7.28 (m, 2H), 3.87-3.83 (s, 3H). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 177.8, 161.5, 154.6, 152.8, 130.2, 127.5, 125.5, 124.4, 122.8, 119.2, 111.4, 52.3. **IR**: 2955(m), 2924(w), 2138(br s, N_2 stretch), 1721(s), 1711(s), 1635(m), 1570(m), 1385(s), 1168(s) cm^{-1}. **HRMS(ESI)** M/Z+ Calc. 244.0484, Obs. 244.0491.

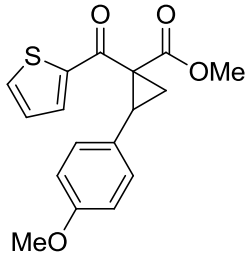


Methyl 3-(2-bromothiophen-3-yl)-2-diazo-3-oxopropanoate (II-51i). According to the general procedure, to a solution of the β-keto ester **II-50i** (0.317 g, 1.21 mmol) in acetonitrile was added Et_3N (0.20 mL, 1.45 mmol) and tosyl azide (0.285 g, 1.45 mmol). Column chromatography (10% EtOAc/Hex, R_f 0.25) furnished **II-51i** as a yellow oil (0.213 g, 61.0%). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.25 (d, *J* = 5.44 Hz, 1H), 7.01 (d, *J* = 5.72 Hz, 1H), 3.79 (s, 3H). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 180.8, 160.8, 138.1, 127.8, 126.1, 114.9, 77.4, 77.0, 76.6, 52.5. **IR**: 3096(w), 2953(w), 2134(br s, N_2 stretch), 1735(s), 1726(s), 1629(s), 1625(m), 1620(m), 1435(m), 1407(m) cm $^{-1}$. **HRMS(ESI)** M/Z+ Calc. 287.9221, Obs. 287.9204.

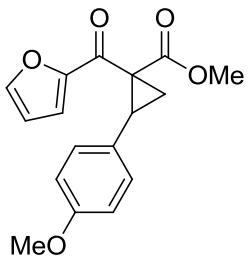
2.8.2.3. General procedure for the formation of cyclopropyl heteroaryl ketones (II-48a to II-48n)[46]

In a flame dried flask containing a solution of Rh_2esp_2 (0.1 mol %) in DCM (0.2M) at 0 °C was added the corresponding alkene (1.0 equiv.). After stirring for 5 minutes, a solution of the α-diazo ester (0.2M) was added in one shot, and allowed to stir for 10 minutes at 0 °C. At this time, the ice bath was removed and the reaction was allowed to warm up to rt. After two hours, the reaction was quenched with saturated aq. thiourea and allowed to stir for 30 minutes. The mixture was transferred to a separatory funnel and extracted with CH_2Cl_2 (3x). The organic layer was washed with brine, dried

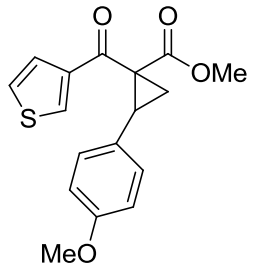
with Na_2SO_4, concentrated, and column chromatography afforded the desired cyclopropyl heteroaryl ketones.



Methyl 2-(4-methoxyphenyl)-1-(thiophene-2-carbonyl)cyclopropanecarboxylate (II-48a). According to the general procedure, to a solution of Rh_2esp_2 (3.8 mg, 5.12 μmol) in DCM was added 4-methoxy styrene (0.68 mL, 5.12 mmol), followed by a solution of α-diazo ester **II-51a** (1.4g, 6.66 mmol). The reaction was quenched and column chromatography (10% EtOAc/Hex) afforded **II-48a** as a solid (1.32 g, 82%). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.49 (dd, *J* = 4.92, 1.11 Hz, 1H), 7.47 (d, *J* = 1.15 Hz, 1H), 7.46 (d, *J* = 1.15 Hz, 1H), 7.00 (d, *J* = 8.70 Hz, 2H), 6.67 (d, *J* = 8.80 Hz, 2H), 3.81 (dd, *J* = 10.96, 5.19 Hz, 3H), 3.71 (s, 3H), 3.41 (dd, *J* = 10.72, 6.55 Hz, 1H), 2.36 (dd, *J* = 8.01, 5.16 Hz, 1H), 1.82 (dd, *J* = 9.26, 5.16 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 186.4, 168.7, 158.7, 143.1, 133.7, 132.4, 130.0, 128.0, 126.5, 113.5, 104.9, 55.1, 52.3, 42.4, 30.0, 19.6. **IR**: 3002(w), 2951(m), 2923(w), 1721(s), 1682(s), 1661(s), 1558(w), 1444(m), 1430(s), 1386(m) cm^{-1}. **HRMS(ESI)** M/Z+ Calc. 316.0762, Obs. 316.0769.

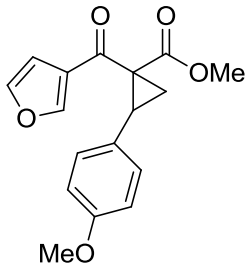


Methyl 1-(furan-2-carbonyl)-2-(4-methoxyphenyl)cyclopropanecarboxylate (II-48b). According to the general procedure, to a solution of Rh_2esp_2 (1.8 mg, 2.36 μmol) in DCM was added 4-methoxy styrene (0.32 g, 2.36 mmol), followed by a solution of the α-diazo ester **II-51b** (0.75g, 3.07 mmol). The reaction was quenched and column chromatography (10% EtOAc/Hex) afforded **II-48b** as a solid (0.467 g, 66 %). (1.5:1 *trans/cis* diastereomeric mixture) **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.67(m, 0.92), 7.58 (m, 0.59), 7.33-7.21 (m, 2.98), 6.99 (dd, *J* = 17.71, 6.22 Hz, 1.02), 6.87 (d, *J* = 6.22 Hz, 2.10), 6.60 (dd, *J* = 3.59, 1.70 Hz, 1.15), 6.35(m,0.80), 3.83 (s, 3.50), 3.70(m, 3.41), 3.51-3.42 (dd, *J* = 17.96, 8.88 Hz, 1.74), 3.40 (s, 3H), 2.40-2.34 (dd, *J* = 8.11, 4.94 Hz, 2.40), 1.67-1.55 (dd, *J* = 9.20, 4.93 Hz, 2.62). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 182.4, 168.5, 158.7, 146.4, 130.0, 129.1, 117.9, 113.4, 112.1, 55.0, 52.4, 41.7, 33.0, 30.0, 20.1, 17.4. **IR**: 3139 (w), 2953(w), 2827(w), 1726(s), 1672(s), 1612(m), 1542 (m), 1513(s), 1436(w), 1309(s), 1248(s), 1159(s) cm^{-1}**. HRMS(ESI)** M/Z+ Calc. 300.1004, Obs. 300.0998.



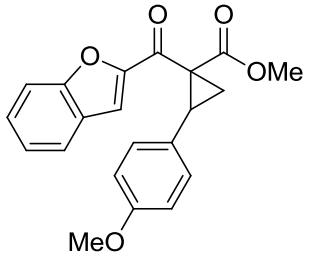
Methyl 2-(4-methoxyphenyl)-1-(thiophene-3-carbonyl)cyclopropanecarboxylate (II-48c). According to the general procedure, to a solution of Rh_2esp_2 (3.6 mg, 4.76 μmol) in DCM was added 4-methoxystyrene (0.49g, 3.65 mmol), followed by a solution of the α-diazo ester **II-51c** (1.0 g, 4.76 mmol). The reaction was quenched and column chromatography (10% EtOAc/Hex) afforded **II-48c** as a solid (0.86 g, 75.0%). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 8.14-8.02 (m, 1H), 7.52 (d, *J* = 3.87 Hz, 1H), 7.33 (d, *J* = 2.59 Hz,

1H), 7.21 (d, *J* = 8.22 Hz, 2H), 6.83 (d, *J* = 8.78 Hz, 2H), 3.78 (s, 3H), 3.33 (s, 3H), 3.44 (t, *J* = 8.56, 8.56 Hz, 1H), 2.32 (dd, *J* = 8.04, 4.92 Hz, 1H), 1.63 (dd, *J* = 9.16, 4.91 Hz, 1H). **^{13}NMR** ($CDCl_3$, 75 MHz) δ 187.980, 169.036, 158.724, 141.255, 132.132, 130.010, 128.928, 127.067, 126.639, 126.322, 113.529, 55.155, 52.312, 43.010, 29.854, 19.739. **IR**: 3113(w), 2947(w), 2831(w), 1726(s), 1671(s), 1665(m), 1608(w), 1552(m), 1513(s), 1117(m), 1034(m)cm^{-1}. **HRMS(ESI)** M/Z+ Calc. 316.0762, Obs. 316.0769.

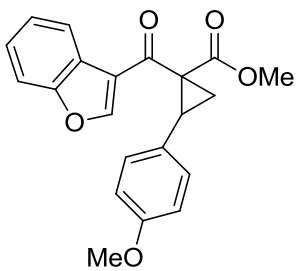


Methyl 1-(furan-3-carbonyl)-2-(4-methoxyphenyl)cyclopropanecarboxylate (II-48d). According to the general procedure, to a solution of Rh_2esp_2 (3.0 mg, 3.96 μmol) in DCM was added the 4-methoxy styrene (0.53 g, 3.96 mmol), followed by a solution of the α-diazo ester **II-51d** (1.0 g, 5.15 mmol). The reaction was quenched and column chromatography (10% EtOAc/Hex) afforded **II-48d** as a yellow solid (0.86 g, 72%). (2.12:1 *tran/cis* diastereomeric mixture) **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 8.02 (s, 0.71), 7.80-7.75 (s, 0.72), 7.54-7.43 (s, 0.85), 7.20-7.05 (m, 1.81), 7.04-6.97 (m, 0.69), 6.87 (dd, *J* = 8.76, 2.83 Hz, 1.37), 6.77 (s, 0.86), 6.65-6.55(m, 0.65), 6.40(s, 0.32), 3.87-3.79 (s, 2.45), 3.60 (t, *J* = 8.58, 8.58 Hz, 1.89), 3.43-3.39 (m, 3.34), 2.31 (ddd, *J* = 7.74, 7.33, 4.87 Hz, 1.13), 1.75(m, 0.47), 1.65 (ddd, *J* = 8.94, 4.89, 3.13 Hz, 1.00). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 188.1, 168.8, 158.7, 147.2, 143.9, 141.7, 140.8, 129.9, 128.9, 126.5, 113.5, 109.1, 55.1, 52.3, 32.9, 29.9, 19.7. **IR**: 3139 (w), 2953(w), 2827(w), 1726(s),

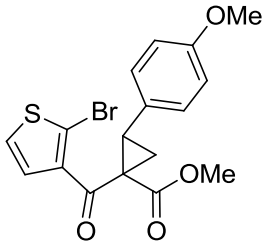
1672(s), 1612(m), 1542 (m), 1513(s), 1436(w), 1309(s), 1248(s), 1159(s) cm^{-1}. **HRMS(ESI)** M/Z+ Calc. 300.1004, Obs. 300.0998.



Methyl 1-(benzofuran-2-carbonyl)-2-(4-methoxyphenyl)cyclopropanecarboxylate (II-48f). According to the general procedure, to a solution of Rh_2esp_2 (1.1 mg, 1.46 µmol) in DCM was added the 4-methoxy styrene (0.2 g, 1.46 mmol), followed by a solution of the α-diazo ester **II-51f** (0.46 g, 1.9 mmol). The reaction was quenched and column chromatography (10% EtOAc/Hex) afforded **II-48f** as a solid (0.323 g, 66.0%). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.71 (d, *J* = 8.51 Hz, 1H), 7.62-7.40 (m, 2H), 7.38-7.15 (m, 2H), 7.02 (d, *J* = 8.84 Hz, 2H), 6.85 (d, *J* = 8.54 Hz, 1H), 6.59 (d, *J* = 8.59 Hz, 1H), 3.80-3.77 (s, 3H), 3.55 (t, *J* = 8.59, 8.59 Hz, 1H), 3.40-3.38 (s 3H), 2.38 (dd, *J* = 8.23, 5.16 Hz, 1H), 1.71 (dd, *J* = 9.37, 5.11 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 184.5, 183.6, 168.5, 158.8, 155.6, 152.1, 130.1, 129.2, 128.3, 128.0, 127.5, 126.4, 123.9, 123.3, 113.4, 112.3, 55.1, 52.6, 42.1, 34.3, 30.2, 20.6. **IR**: 2940(w), 2831(w), 1721(s), 1658(s), 1513(s), 1432(m), 1246(s), 1246(m), 1162(m) cm^{-1}. **HRMS(ESI)** M/Z+ Calc. 350.1154, Obs. 350.1163.

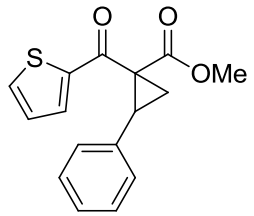


Methyl 1-(benzofuran-3-carbonyl)-2-(4-methoxyphenyl)cyclopropanecarboxylate (II-48h). According to the general procedure, to a solution of Rh_2esp_2 (2.2 mg, 2.9 μmol) in DCM was added the 4-methoxy styrene (0.4 g, 2.92 mmol), followed by a solution of the α-diazo ester **II-51h** (0.92 g, 3.8 mmol). The reaction was quenched and column chromatography (10% EtOAc/Hex) afforded **II-48h** (0.646 g, 66.0%). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.71 (d, *J* = 7.86 Hz, 1H), 7.65-7.38 (m, 2H), 7.38-7.14 (m, 2H), 7.02 (d, *J* = 8.86 Hz, 1H), 6.84 (d, *J* = 8.76 Hz, 2H), 6.71-6.45 (m, 1H), 3.81-3.77 (s, 3H), 3.58-3.47 (m, 1H), 3.40-3.36 (s, 3H), 2.38 (dd, *J* = 8.19, 4.97 Hz, 1H), 1.70 (dd, *J* = 9.23, 4.97 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 184.5, 168.4, 158.8, 155.6, 151.9, 130.1, 129.3, 128.3, 128.0, 123.9, 123.4, 113.6, 113.5, 112.4, 55.2, 55.0, 52.4, 42.0, 33.4, 30.3, 20.5. **IR**: 2940(w), 2840(w), 1729(s), 1737(s), 1672(s), 1553(m), 1514(s), 1442(m), 1305(m), 1282(m), 1248(m) cm $^{-1}$. **HRMS(ESI)** M/Z+ Calc. 350.1154, Obs. 350.1163.

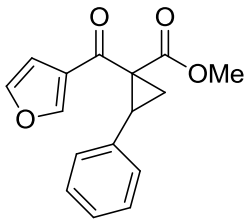


Methyl-1-(2-bromothiophene-3-carbonyl)-2-(4-methoxyphenyl)cyclopropane carboxylate(II-48i). According to the general procedure, to a solution of Rh_2esp_2 (0.51 mg, 6.65 μmol) in DCM was added the 4-methoxy styrene (0.089 g, 0.665 mmol), followed by a solution of the α-diazo ester **II-51i** (0.25 g, 0.864 mmol). The reaction was quenched and column chromatography (10% EtOAc/Hex) afforded **II-48i** as a solid (0.15g, 57.0%). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.28 (d, *J* = 8.77 Hz, 1H), 7.19-7.12 (m, 2H), 7.03-6.94 (m, 1H), 6.82 (d, *J* = 8.77 Hz, 2H), 3.71 (s, 3H), 3.56 (s, 3H), 3.38 (dd, *J*

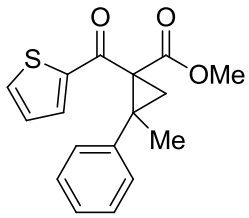
= 15.27, 10.72 Hz, 1H), 3.03 (dd, *J* = 15.27, 8.99 Hz, 1H), 2.36-2.25 (m, 1H), 1.64 (dd, *J* = 8.89, 5.15 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 165.0, 159.6, 133.0, 130.1, 129.1, 128.7, 128.0, 127.5, 126.3, 125.6, 125.5, 114.0, 55.3, 51.2, 38.5, 32.0, 21.5. **IR**: 3103(w), 2933(m), 2827(w), 1688(m), 1602(w), 1512(s), 1429(m), 1245(s), 1167(m), 1110(m), 1088(w), 1031(m) cm^{-1}. **HRMS(ESI)** M/Z+ Calc. 393.9841, Obs. 393.9831.



Methyl 2-phenyl-1-(thiophene-2-carbonyl)cyclopropanecarboxylate (II-48j). According to the general procedure, to a solution of Rh_2esp_2 (0.83 mg, 0.1 mol %) in DCM was added styrene (0.113 g, 1.09 mmol), followed by a solution of the α-diazo ester **II-51a** (0.30 g, 1.43 mmol). The reaction was quenched and column chromatography (10% EtOAc/Hex) afforded **II-48j** as a solid (0.198 g, 81.0 %). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.72 (d, *J* = 1.13 Hz, 1H), 7.67-7.65 (d, *J* = 1.12 Hz, 1H), 7.45-7.30 (d, *J* = 1.12 Hz, 5H), 7.05-7.00 (m,1H), 3.49 (dd, *J* = 8.98, 8.32 Hz, 1H), 3.37-3.28 (s, 3H), 2.38 (dd, *J* = 8.10, 5.05 Hz, 1H), 1.67 (dd, *J* = 9.17, 5.04 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 186.226, 168.651, 143.043, 134.674, 133.877, 132.471, 128.982, 128.101, 127.530, 127.245, 52.345, 42.519, 30.402, 19.427. **IR**: 3036 (w), 2947(w), 1745(s), 1656 (s), 1409(s), 1271(s), 1141(s), 1197(s), 1040(s), 957(s) cm^{-1}. **HRMS(ESI)** M/Z+ Calc. 286.0670, Obs. 286.0697

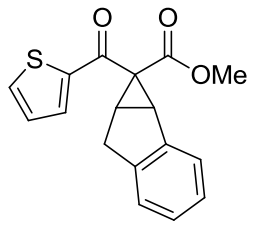


Methyl 1-(furan-3-carbonyl)-2-phenylcyclopropanecarboxylate(II-48k): According to the general procedure, to a solution of Rh_2esp_2 (1.1 mg, 1.19 μmol) in DCM was added the styrene (0.154 g, 1.83 mmol), followed by a solution of the α-diazo ester **II-51d** (0.30 g, 1.54 mmol). The reaction was quenched and column chromatography (10% EtOAc/Hex) afforded **II-48k** as an oil (0.18 g, 43.0%). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 8.02 (dd, *J* = 1.46, 0.86 Hz, 1H), 7.43 (dd, *J* = 1.93, 1.47 Hz, 1H), 7.32-7.20 (m, 5H), 6.76 (dd, *J* = 1.94, 0.85 Hz, 1H), 3.55-3.42 (m, 1H), 3.34 (s, 3H), 2.31 (dd, *J* = 8.05, 4.95 Hz, 1H), 1.62 (dd, *J* = 9.15, 4.95 Hz, 1H)). **^{13}H NMR** ($CDCl_3$, 75 MHz) δ 187.9, 168.7, 147.2 (2C), 143.9(2C), 134.6, 128.8, 128.1, 127.2, 126.7, 109.0, 52.2, 43.3, 30.2, 19.5. **IR**: 3121.1(m), 2990.4(w), 1844.1 (w), 1829(m), 1772.1(s), 1700.0(s), 1684.0(m), 1665.8(m), 1635.8(w) cm^{-1}. **HRMS (ESI)** Calc. 270.0892, Obs. 270.0893.

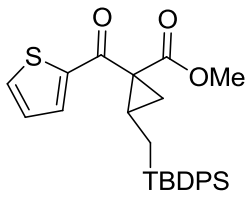


Methyl 2-methyl-2-phenyl-1-(thiophene-2-carbonyl)cyclopropanecarboxylate(II-48l). According to the general procedure, to a solution of Rh_2esp_2 (0.83 mg, 1.09 μmol) in DCM was added the alpha methyl styrene (0.13 g, 1.09 mmol), followed by a solution of the α-diazo ester **II-51a** (0.30 g, 1.43 mmol). The reaction was quenched and column chromatography (10% EtOAc/Hex) afforded **II-48l** as a solid (0.21 g, 65.0%). **^{1}H NMR**

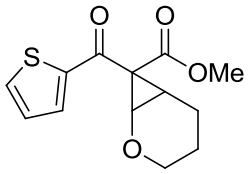
($CDCl_3$, 300 MHz) δ 7.90 (dd, *J* = 3.81, 1.15 Hz, 1H), 7.69 (dd, *J* = 4.95, 1.15 Hz, 1H), 7.43-7.38 (m, 5H), 7.19 (dd, *J* = 4.94, 3.82 Hz, 1H), 3.38-3.33 (s, 3H), 2.35 (d, *J* = 4.98 Hz, 1H), 1.81 (d, *J* = 4.98 Hz, 1H), 1.43-1.40 (s, 3H). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 186.157, 169.698, 145.168, 141.387, 134.034, 133.560, 128.351(2C), 128.191(2C), 128.106, 127.079, 52.259, 43.701, 37.888, 25.659, 25.165. **IR**: 3002 (w), 2951(w), 2923(w), 1721(s), 1682(s), 1661(s), 1515(w), 1444(s) 1410(m) cm^{-1}. **HRMS(ESI)** M/Z+ Calc. 300.0820, Obs. 300.0830.



Methyl-1-(thiophene-2-carbonyl)-1,1a,6,6a-tetrahydrocyclopropa[a]indene-1-carboxylate(II-48m). According to the general procedure, to a solution of Rh_2esp_2 (1.08 mg, 1.43 μmol) in DCM was added indene (0.128 g, 1.10 mmol), followed by the α-diazo ester **II-51a** (0.30 g, 1.43 mmol). The reaction was quenched and column chromatography (10% EtOAc/Hex) afforded **II-48m** as an oil (0.20 g, 62%). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.90-7.75 (m, 1H), 7.70 (ddd, *J* = 4.98, 1.45, 0.84 Hz, 1H), 7.55-7.33 (m, 1H), 7.30-7.19 (m, 3H), 7.19-7.07 (m, 1H), 3.69 (ddd, *J* = 18.20, 12.11, 0.73 Hz, 1H), 3.48-3.30 (m, 1H), 3.30 (dd, *J* = 2.31, 1.77 Hz, 1H), 2.74 (dt, *J* = 6.54, 6.54, 0.74 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 186.0, 167.8, 143.6, 143.2, 139.3, 134.0, 132.3, 128.2, 127.1, 126.6, 125.3, 124.4, 52.0, 44.6, 39.5, 33.6, 33.6. **IR**: 3060(w), 2943(m), 1735(s), 1657(s), 1648(s), 1640(s), 1434(w), 1410(s), 1353(m), 1301(s), 1264(s) cm^{-1}. **HRMS(ESI)** M/Z+ Calc. 298.0670, Obs. 298.0697

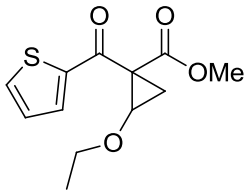


Methyl 2-((tert-butyldiphenylsilyl)methyl)-1-(thiophene-2-carbonyl) cyclopropane carboxylate (II-48n). According to the general procedure, to a solution of Rh_2esp_2 (1.4 mg, 1.83 μmol) in DCM was added TBDPS allylsilane (0.513 g, 1.83 mmol), followed by a solution of the α-diazo ester **II-51a** (0.50 g, 2.40 mmol). The reaction was quenched and column chromatography (10% EtOAc/Hex) afforded **II-48n** as an oil (0.375 g, 44.3%). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.66 (dd, *J* = 7.54, 1.90 Hz, 4H), 7.62-7.54 (m, 3H), 7.45-7.30 (m, 4H), 7.06 (dd, *J* = 4.83, 3.95 Hz, 2H), 3.66 (s, 3H), 2.20-1.99 (m, 1H), 1.62 (dd, *J* = 14.80, 3.19 Hz, 1H), 1.45-1.23 (m, 1H), 1.16 (dd, *J* = 9.13, 4.77 Hz, 1H), 1.10 (s, 9H). **^{13}H NMR** ($CDCl_3$, 75 MHz) δ 186.9, 170.2, 143.3, 135.9, 135.9, 134.1, 133.8, 133.2, 131.9, 129.1, 129.1, 127.8, 127.6, 127.5, 52.3, 40.2, 27.7, 24.1, 23.4, 18.0, 8.2. **IR**: 3013.6, 2928.5, 2855.8, 1725.4, 1657.7, 1457.5, 1426.9, 1310.2, 1275.3 cm^{-1}. **HRMS (ESI)** Calc. 462.1719, Obs. 462.1681.

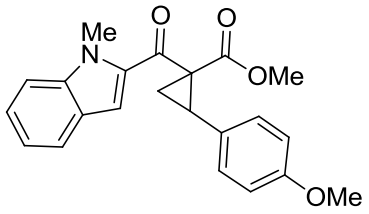


Methyl 7-(thiophene-2-carbonyl)-2-oxabicyclo[4.1.0]heptane-7-carboxylate(II-48o): According to the general procedure, to a solution of Rh_2esp_2 (1.4 mg, 1.83 μmol) in DCM was added the dihydropyran (0.154 g, 1.83 mmol), followed by a solution of the α-diazo ester **II-51a** (0.50 g, 2.37 mmol). The reaction was quenched and column chromatography (10% EtOAc/Hex) afforded **II-48o** as an oil (0.32 g, 66 %). **^{1}H NMR**

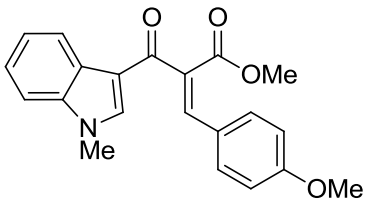
($CDCl_3$, 300 MHz) δ 7.77 (dd, *J* = 3.85, 1.13 Hz, 1H), 7.66 (dd, *J* = 4.95, 1.13 Hz, 1H), 7.18-7.06 (m, 1H), 6.52 (s, 1H), 4.68 (s, 1H), 4.00-3.90 (m, 1H), 3.74 (s, 3H), 3.71-3.64 (m, 1H), 2.43-2.19 (m, 1H), 2.14-1.94 (m, 1H), 1.96-1.72 (m, 1H). **^{13}H NMR** ($CDCl_3$, 75 MHz) δ 186.7, 169.3, 144.8, 142.4, 134.5, 132.9, 128.2, 106.9, 65.7, 58.7, 52.4, 22.0, 21.4. **IR**: 3137.0(m), 2950.9(m), 1734.5(s), 1727.2(m), 1672.2(s), 1462.0(m) cm^{-1}. **HRMS (ESI)** Calc. 266.0647, Obs. 266.0624.



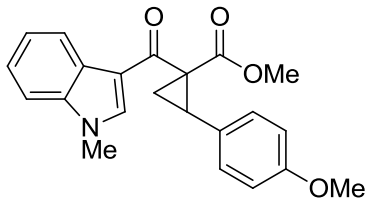
Methyl 2-ethoxy-1-(thiophene-2-carbonyl)cyclopropanecarboxylate (II-48p): According to the general procedure, to a solution of Rh_2esp_2 (1.8 mg, 2.37 μmol) in DCM at 0 °C was added the ethyl vinyl ether (0.132 g, 1.83 mmol), followed by a solution of the α-diazo ester **II-51a** (0.50 g, 2.37 mmol). The reaction was quenched and column chromatography (10% EtOAc/Hex) afforded **II-48p** as an oil (0.43 g, 72 %). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 8.20 (d, *J* = 3.82 Hz, 1H), 7.46 (dd, *J* = 5.05, 1.15 Hz, 1H), 7.06 (dd, *J* = 5.05, 3.87 Hz, 1H), 5.57 (dd, *J* = 7.16, 2.58 Hz, 1H), 3.89 (qd, *J* = 9.57, 7.08, 7.08, 7.07 Hz, 1H), 3.71 (s, 3H), 3.60 (qd, *J* = 9.57, 7.08, 7.08, 7.07 Hz, 2H), 3.20 (dd, *J* = 16.75, 7.17 Hz, 1H), 2.92 (dd, *J* = 16.75, 2.56 Hz, 1H), 1.21 (t, *J* = 7.09, 7.09 Hz, 3H). **^{13}H NMR** ($CDCl_3$, 75 MHz) δ 165.1, 156.7, 132.1, 131.4, 130.1, 127.1, 104.0, 99.8, 77.6, 77.2, 76.7, 64.1, 51.0, 38.2, 15.1. **IR**: 3138.1(w), 2950.9(w), 1736.7(s), 1726.4(s), 1672.2(s), 1506.8(m), 1462.2(m) cm^{-1}. **HRMS (ESI)** Calc. 252.0456 Obs. 252.0462.



Methyl 2-(4-methoxyphenyl)-1-(1-methyl-1H-indole-2-carbonyl)cyclopropane carboxylate (II-48e). *t*-BuLi (1.3 mL, 1.70 mmol) was added over 15 minutes to a -78°C solution of *n*-methyl indole (0.24 mL, 1.87 mmol) in THF (8.52 mL). After stirring for 45 minutes at -78 °C, a solution of the Weinreb amide cyclopropane (0.250 g, 0.852 mmol) in 2 mL THF was added slowly to the reaction and allow to warm up to rt. After 3 hours, the reaction was quenched with saturated aqueous NH_4Cl, extract 3x with Et_2O, dried with Na_2SO_4, and column chromatography (10 % EtOAc/Hex, R_f 0.25) afforded cyclopropane **II-48e** (0.21 g, 68%). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.69 (ddd, *J* = 11.39, 5.62, 4.54 Hz, 1H), 7.46-7.27 (m, 3H), 7.12 (d, *J* = 9.50 Hz, 2H), 6.83 (d, *J* = 8.76 Hz, 1H), 6.71 (d, *J* = 8.75 Hz, 2H), 4.07 (s, 3H), 3.81 (s, 3H), 3.71 (s, 3H), 3.51-3.37 (m, 1H), 3.18-3.02 (m, 1H), 2.77 (dd, *J* = 16.96, 8.66 Hz, 1H), 2.39 (dd, *J* = 8.03, 5.07 Hz, 1H), 1.99 (dd, *J* = 12.26, 5.65 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 186.9, 169.2, 158.6, 139.9, 138.7, 130.0, 126.8, 123.0, 122.3, 121.0, 119.8, 113.5, 111.6, 110.3, 103.5, 55.1, 52.4, 43.2, 32.0, 32.0, 29.1, 19.8. **IR**: 2924.2, 1728.3, 1699.8, 1684.1, 1656.3, 1363.5, 1248.3 cm^{-1}. **HRMS (ESI)** Calc. 363.1471, Obs. 363.1479.



Methyl 3-(4-methoxyphenyl)-2-(1-methyl-1H-indole-3-carbonyl)acrylate.[37] A solution of the *β*-ketoester **II-50g** (0.75 g, 3.24 mmol), *p*-anisaldehyde (0.56 g, 4.09 mmol), glacial acetic acid (80 µL, 1.49 mmol), piperidine (32 µL, 0.324 mmol) was refluxed in benzene (30 mL) using a Dean-Stark apparatus for 16 hours. The residual dark red brown mixture was dissolved in de-ionized water and extracted with ethyl acetate (3x). The combined organic layers were then washed with 1N hydrochloric acid followed by a subsequent wash with saturated sodium bicarbonate solution. The mixture was concentrated under high vacuum after drying with magnesium sulfate. Column chromatography (25% EtOAc/Hex) furnished the desired alkenyl substrate as an orange oil (0.724 g, 63%). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.91-7.79 (m, 1H), 7.59-7.50 (m, 1H), 7.45 (d, *J* = 8.95 Hz, 2H), 7.40-7.27 (m, 4H), 6.71 (d, *J* = 8.89 Hz, 2H), 3.74 (s, 3H), 3.70 (s, 3H), 3.70 (s, 3H). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 189.2, 166.5, 161.1, 141.0, 138.0, 137.8, 132.4, 129.7, 126.2, 125.7, 123.7, 122.9, 122.6 (2C), 116.3, 114.2, 109.8, 55.2, 52.4, 33.6. **IR**: 3051.8, 2949.5, 2182.9, 2055.7, 1709.6, 1599.3, 1511.5, 1250.3, 1173.6 cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 349.1314, Obs. 349.1307.



Methyl 2-(4-methoxyphenyl)-1-(1-methyl-1H-indole-3-carbonyl)cyclopropane carboxylate (II-48g).[34] Following a Waser's protocol, *n*-BuLi (0.858 mmol) was added dropwise to a solution of trimethylsulfoxonium iodide (0.193 g, 0.944 mmol) in anhydrous THF (0.75 M) at 0 °C. The solution was allowed to warm to rt and stirring was continued under nitrogen for 1 hour. A solution of the 0.54 M of ylide was obtained. The

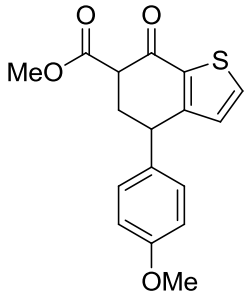
ylide (1.74 mL, 0.943 mmol) was added dropwise to a solution of the alkene (0.300g, 0.858 mmol) in anhydrous THF (0.10 M) at rt and stirred for 3 hours. The reaction was quenched with $NaHCO_3$ and extracted with Et_2O (3x). The combined organic layers were washed with brine (2x), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Column chromatography (10% EtOAc/Hex, R_f 0.15) afforded the indolyl cyclopropane **II-48g** (0.168 g, 54.0%). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 8.94 (s, 1H), 8.16 (ddd, *J* = 7.74, 1.39, 0.75 Hz, 1H), 6.84 (d, *J* = 8.76 Hz, 2H), 7.40-7.24 (m, 3H), 7.22 (d, *J* = 8.74 Hz, 2H), 4.88 (dd, *J* = 9.75, 8.95 Hz, 1H), 4.51 (dd, *J* = 8.92, 3.86 Hz, 1H), 4.43 (dd, *J* = 9.77, 3.83 Hz, 1H), 3.87 (s, 3H), 3.79 (s, 3H), 3.60 (s, 3H), 1.84(m,1H). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 187.5, 169.9, 158.5, 137.3, 135.5, 129.9, 127.3, 126.6, 123.5, 122.8, 122.5, 115.4, 113.4, 109.6, 55.1, 52.3, 43.1, 33.6, 28.6, 18.7. **IR**: 2924.2, 1728.3, 1699.8, 1684.1, 1656.3, 1363.5, 1248.3 cm^{-1}. **HRMS (ESI)** Calc. 363.1471, Obs. 363.1479.

2.8.2.4. Procedure for Catalyst Screening

To a flame dried flask containing the indium catalyst with the appropriate loading (1, 5, or 30 mol%) in anhydrous CH_2Cl_2 (0.2 M) was added cyclopropane **II-48a**. The reaction was monitored via TLC, and upon complete disappearance of the starting material, the reaction was quenched with H_2O. The mixture was extracted with CH_2Cl_2, dry with Na_2SO_4, and column chromatography (10% EtOAc/Hex) provided **II-49a**.

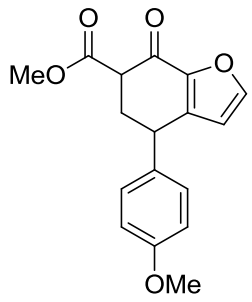
2.8.2.5. General Procedure for the Lewis-Acid catalyzed cyclization of heteroaryl cyclopropyl ketones (II-48a to II-48n)

To a flame dried flask containing $In(OTf)_3$ (5 mol %) in anhydrous CH_2Cl_2 (0.2M) was added the corresponding cyclopropane. The reaction was monitored via TLC, and upon complete disappearance of the starting material, the reaction was quenched with H_2O. The mixture was extracted with CH_2Cl_2, dried with Na_2SO_4, and column chromatography provided the fused heteroaromatic cyclohexanones.

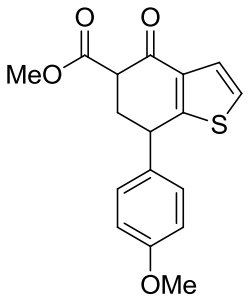


Methyl-4-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-6 carboxylate (II-49a). According to the general procedure, a solution of $In(OTf)_3$ (4.42 mg, 8.33 µmol) in DCM was added cyclopropane **II-48a** (0.050 g, 0.17 mmol). The reaction was quenched after 4.5 h, and column chromatography (15% EtOAc/Hex, R_f 0.25) provided **II-49a** as a solid (0.043 g, 86.4%). (*Diastereomeric ratio 1.5:1*) **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.64 (d, *J* = 4.94 Hz, 0.90), 7.59 (d, *J* = 4.93 Hz, 1.13), 7.13 (d, *J* = 8.48 Hz, 2.82), 7.03 (d, *J* = 8.55 Hz, 2.02), 6.88 (dd, *J* = 10.85, 8.57 Hz, 4.46), 6.71 (d, *J* = 5.00 Hz, 0.90), 6.58 (d, *J* = 5.01 Hz, 1.14), 4.38 (dd, *J* = 7.49, 4.81 Hz, 1.00), 4.10 (dd, *J* = 11.85, 4.48 Hz, 1.52), 3.82-3.73 (m, 15.44), 3.68 (dd, *J* = 7.19, 4.84 Hz, 1H), 2.92-2.62 (m, 2.72), 2.58-2.32 (m, 2.32). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 165.3, 159.8, 133.0, 130.1, 129.1, 127.5(2C), 125.4, 114.0(2C), 113.5, 104.9, 83.7, 55.3, 55.1, 51.2, 38.5. **IR**: 3086(w), 2950(m), 2827(w), 1736(s), 1664(s), 1602(w), 1510(m),

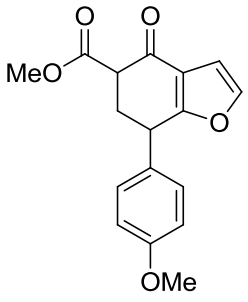
1413(s), 1244(s), 1175(s), 1151(s), 1014(m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 316.0769, Obs. 316.0771.



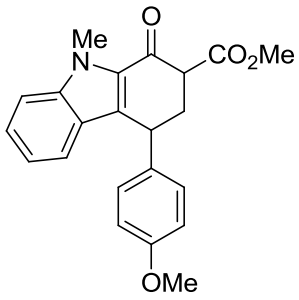
Methyl 4-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydrobenzofuran-6-carboxylate (II-49b). A solution of $In(OTf)_3$ (8.15 mg, 0.015 mmol) in DCE was added cyclopropane **II-48b** (0.088 g, 0.29 mmol) and the reaction was heated to reflux. After 6 h, the reaction was cooled to room temperature, followed by the general work up. Column chromatography (15% EtOAc/Hex, R_f 0.25) provided **II-49b** as a solid (0.059 g, 67.0 %). (*Diastereomeric ratio 1.1:1*) **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.38-7.30 (m, 1.91), 7.14-7.08 (d, *J* = 0.58 Hz, 1.98), 7.04-7.01 (d, *J* = 0.58 Hz, 2.24), 6.92-6.86 (m, 4.29), 6.76-6.72 (m, 2.02), 4.53-4.39 (m, 1.00), 4.30-4.19 (m, 0.95), 3.82-3.78 (m, 6.23), 3.76-3.70(m, 6.28), 3.68-3.58(m, 2.56), 2.91-2.83 (m, 1.23), 1.30-1.18 (m, 2.27), 2.40-2.30(m, 1.22). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 187.7, 170.9, 166.8, 159.1, 151.0, 129.8, 128.8, 114.3, 113.9, 110.9, 106.9, 104.8, 55.3, 54.4, 52.4, 51.6, 51.3, 40.2, 35.5, 29.7, 22.7. **IR**: 3116 (w), 2947(w), 2824(w), 1735(m), 1685(s), 1602(m), 1525(m), 1439(m), 1247(br s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 300.1004, Obs. 300.0998.



Methyl-7-(4-methoxyphenyl)-4-oxo-4,5,6,7-tetrahydrobenzo[b]thiophene-5-carboxylate (II-49c). According to the general procedure, a solution containing $In(OTf)_3$ (8.9 mg, 0.158 mmol) was added cyclopropane **II-48c** (0.10 g, 0.316 mmol). The reaction was quenched after 5 h, and column chromatography (15% EtOAc/Hex, R_f 0.25) provided **II-49c** as a solid (0.073 g, 73.0%). (*Diastereomeric ratio 1.7:1*) **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.45-7.36 (m, 1.96), 7.21-7.11 (m, 2.65), 7.10-7.00 (m, 2.67), 6.99-6.80 (m, 3.59), 4.55 (dd, *J* = 8.04, 4.66 Hz, 0.58), 4.29 (dd, *J* = 11.87, 4.30 Hz, 1.00), 3.80-3.56 (m, 13.8), 2.93-2.67 (m, 2.11), 2.62-2.39 (m, 2.04). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 187.6, 170.4, 161.6, 159.2, 135.9, 134.4, 129.1, 128.9, 124.9, 114.2, 55.3, 52.5, 42.4, 42.6, 39.6, 37.0. **IR**: 3086(w), 2950(m), 2827(w), 1736(s), 1664(s), 1602(w), 1510(m), 1413(s), 1244(s), 1175(s), 1151(s), 1014(m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 316.0769, Obs. 316.0771.

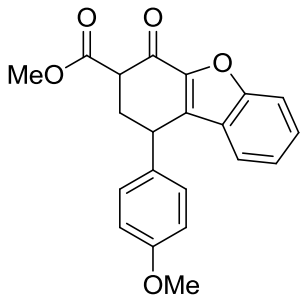


Methyl 7-(4-methoxyphenyl)-4-oxo-4,5,6,7-tetrahydrobenzofuran-5-carboxylate (II-49d). According to the general procedure, to a solution containing $In(OTf)_3$ (9.36 mg, 0.017 mmol) was added cyclopropane **II-48d** (0.100 g, 0.33 mmol). The reaction was quenched after 6 h, and column chromatography (15% EtOAc/Hex, R_f 0.25) provided **II-49d** as a solid (0.073 g, 73.0%). (*Diastereomeric ratio 1.1:1*) **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.36 (d, *J* = 2.05 Hz, 1.03), 7.32 (dd, *J* = 1.45, 0.60 Hz, 1.12), 7.17-7.07 (m, 2.32), 7.06-6.98 (m, 2.21), 6.96-6.84 (m, 4.31), 6.74-6.70 (m, 2.20), 4.46 (dd, *J* = 3.76, 3.07 Hz, 1.00), 4.24 (dd, *J* = 10.49, 5.79 Hz, 1.09), 3.84-3.72 (m, 12.77), 3.72-3.54 (m, 3.25), 2.87 (s, 1.29), 2.75-2.46 (m, 2.61), 2.46-2.26 (m, 1.44). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 188.7, 170.0, 167.2, 159.2, 144.1, 131.0, 129.1, 128.6, 121.1, 114.5, 106.8, 55.3, 54.5, 52.6, 52.4, 51.6, 40.5, 37.9, 36.0, 35.5. **IR**: 3060(w), 2947(w), 2834(w), 1745(m), 1687(s), 1679(m), 1442(m), 1264(s), 1249(s), 1180(w), 1117(w), 1027(w) cm $^{-1}$. **HRMS (ESI)** M/Z+ Calc. 300.0998, Obs. 300.0998.



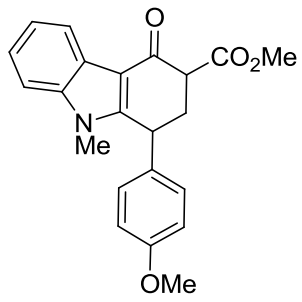
Methyl-4-(4-methoxyphenyl)-9-methyl-1-oxo-2,3,4,9-tetrahydro-1H-carbazole-2-carboxylate (II-49e). According to the general procedure, to a solution containing $In(OTf)_3$ (3.85 mg, 6.85 µmol) was added cyclopropane **II-48e** (0.049 g, 0.137 mmol). The reaction was quenched after 5.5 h, and column chromatography (20% EtOAc/Hex, R_f 0.20) provided **II-49e** as a solid (0.031 g, 63.0 %). (*Diastereomeric ratio 1.2:1*) **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.41-7.33 (m, 3.96), 7.33-7.28 (m, 2.23), 7.16 (d, *J* = 8.63

Hz, 2.81), 7.12-7.01 (m, 1.29), 6.96-6.81 (dd, *J* = 7.89, 4.16 Hz, 4.52), 6.69 (td, *J* = 8.18, 0.95, 0.95 Hz, 1.06), 4.62 (t, *J* = 5.63, 5.63 Hz, 1.00), 4.37 (dd, *J* = 11.21, 4.71 Hz, 1.21), 4.09 (d, *J* = 9.30 Hz, 4.97), 3.80-3.60 (m, 12.85), 2.99-2.84 (m, 1.39), 2.60-2.48 (m, 2.52), 2.40 (m, 1.63). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 186.9, 170.7, 158.6, 140.4, 135.2, 134.2, 131.1, 130.3, 127.0, 124.3, 122.9, 120.1, 114.0, 110.3, 55.6, 52.4, 40.4, 38.5, 37.4, 31.6. **IR**: 3030.6, 2924.2, 2850.4, 1791.7, 1771.8, 1737.9, 1657.6, 1623.3 1518.8, 1540.0, 1511.3, 1246.4, 1246.4 cm $^{-1}$. **HRMS (ESI)** Calc. 363.1471 Obs. 363.1478.

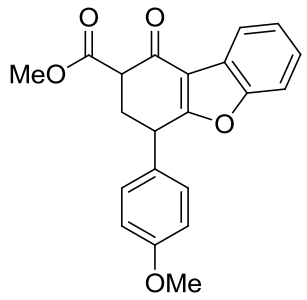


Methyl 1-(4-methoxyphenyl)-4-oxo-1,2,3,4-tetrahydrodibenzo[b,d]furan-3-carboxylate (II-49ff). According to the general procedure, a solution containing $In(OTf)_3$ (6.55 mg, 0.017 mmol) was added the cyclopropane **II-48f** (0.078 g, 0.233 mmol). The reaction was quenched after 5 h, and column chromatography (15% EtOAc/Hex, R_f 0.25) provided **II-49f** as a solid (0.071 g, 91.0%). (*Diastereomeric ratio 1.4:1*) **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.57 (dd, *J* = 8.45, 3.57 Hz, 2.41), 7.47-7.40 (m, 2.73), 7.22-7.01 (m,5.41), 6.90-6.70 (dd, *J* = 14.89, 6.23 Hz, 4.67), 4.60 (dd, *J* = 8.46, 4.96 Hz, 1.00), 4.38 (dd, *J* = 10.88, 4.98 Hz, 0.73), 3.90-3.80 (m, 12.35), 3.77-3.74 (m, 3H), 2.91 (m, 1.19), 2.69-2.56 (m, 1.94), 2.56-2.41 (m, 1.37). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 224.963, 158.994, 156.447, 133.151, 132.548, 129.394, 128.978, 125.526, 123.590, 123.286, 114.303, 112.833, 55.294, 52.639, 52.351, 39.608, 37.871. **IR**: 2942(w), 2831(w),

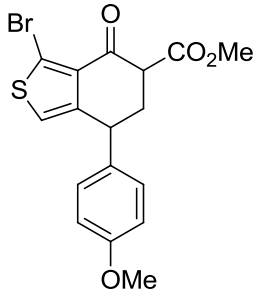
1731(s), 1677(s), 1608(s), 1511(s), 1426(m), 1245(s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 350.1154, Obs. 350.1163.



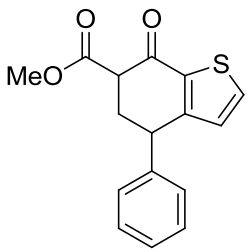
Methyl-1-(4-methoxyphenyl)-9-methyl-4-oxo-2,3,4,9-tetrahydro-1H-carbazole-3-carboxylate (II-49g). According to the general procedure, to a solution containing $In(OTf)_3$ (2.86 mg, 5.0 µmol) was added cyclopropane **II-48g** (0.037 g, 0.102 mmol). The reaction was quenched after 6 h, and column chromatography (20% EtOAc/Hex, R_f 0.25) provided **II-49g** as a solid (0.022 g, 61.0%). (*Diastereomeric ratio 1.2:1*) **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.36-7.30 (d, *J* = 3.34 Hz, 3.70), 7.18-7.10 (d, *J* = 8.60 Hz, 3.50), 7.07-7.00 (m, *J* = 8.64 Hz, 2.68), 6.98 (dd, *J* = 8.02, 3.98 Hz, 0.92), 6.93-6.78 (m, 4.05), 4.64 (t, *J* = 5.61, 5.61 Hz, 1.00), 4.38 (dd, *J* = 10.76, 5.06 Hz, 0.87), 4.12 (m, 4.68), 3.82-3.70 (m, 11.75), 2.93 (ddd, *J* = 13.51, 8.75, 5.04 Hz, 1.20), 2.49-2.36(m, 3.14). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 187.1, 171.0, 158.5, 135.2, 134.2, 130.3, 129.2, 127.0, 122.9, 122.3, 120.3, 120.1, 114.0, 110.3, 55.6, 52.2, 40.3, 38.5, 37.4, 36.9, 31.6, 29.6. **IR**: 3000.6, 2924.2, 2850.4, 1791.7, 1737.9, 1657.6, 1623.4, 1540.0, 1511.3, 1246.4, 1218.7 cm^{-1}. **HRMS (ESI)** Calc. 363.1471 Obs. 363.1478.



Methyl 4-(4-methoxyphenyl)-1-oxo-1,2,3,4-tetrahydrodibenzo[b,d]furan-2-carboxylate (II-49h). According to the general procedure, to a solution containing $In(OTf)_3$ (5.8 mg, 0.103 µmol) was added cyclopropane **II-48h** (0.075 g, 0.206 mmol). The reaction was quenched after 5.5 h, and column chromatography (15% EtOAc/Hex, R_f 0.25) provided **II-49h** as a solid (0.053 g, 71.0%). (*Diastereomeric ratio 1.2:1*) **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.61-7.52 (m, 2.40), 7.50-7.42 (dd, *J* = 13.96, 7.11 Hz,2.73), 7.22-7.00 (m, 6.82), 6.95-6.82 (m, 5.51), 6.77-6.69 (m, 1.16), 4.65-4.55(m, 1.00), 4.36 (dd, *J* = 10.80, 4.86 Hz, 1.21), 3.90-3.70 (m, 15.76), 2.96-2.84 (m, 1.15), 2.80-2.56 (m, 2.66), 2.53-2.40 (m, 1.25). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 182.8, 169.8, 169.6, 159.0, 158.9, 156.4, 146.0, 136.9, 132.6, 129.4, 129.2, 125.6, 123.7, 123.6, 114.3, 112.8, 55.3, 54.5, 52.3, 39.6, 38.0. **IR**: 2960(m), 2923(m), 2844(w), 1721(s), 1675(m), 1615(w), 1552(m), 1505(w), 1459(m), 1426(m) cm $^{-1}$. **HRMS (ESI)** M/Z+ Calc. 350.1154, Obs. 350.1163.

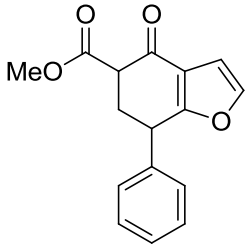


Methyl 3-bromo-7-(4-methoxyphenyl)-4-oxo-4,5,6,7-tetrahydrobenzo[c]thiophene-5-carboxylate (II-49i). According to the general procedure, to a solution containing $In(OTf)_3$ (3.55 mg, 6.32 µmol) was added cyclopropane **II-48i** (0.050 g, 0.126 mmol). The reaction was quenched after 8 h, and column chromatography (15% EtOAc/Hex, R_f 0.25) provided **II-49i** as a solid (0.028 g, 56.0 %). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.16 (d, *J* = 8.80 Hz, 1H), 6.96-6.79 (m, 1H), 6.45-6.40 (m, 1H), 3.95-3.84 (m, 1H), 3.83-3.77 (s, 3H), 3.79-3.73 (s, 3H), 2.91-2.76 (m, 1H), 2.70-2.55 (m, 1H). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 173.0, 163.1, 158.7, 146.7, 144.7, 133.8, 131.8, 130.0, 129.2, 122.7, 121.2, 114.3, 57.4, 56.6, 55.3, 51.8, 43.0, 30.8. **IR**: 2920(m), 2840(m), 1735(m), 1598(m), 1511(s), 1440(m), 1353(m), 1246(s), 1176(m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 393.9841, Obs. 393.9869.

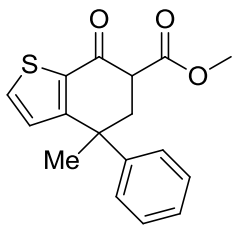


Methyl 7-oxo-4-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-6-carboxylate (II-49j): A solution containing $In(OTf)_3$ (5.2 mg, 9.24 µmol) in DCE was added cyclopropane **II-48j** (0.050 g, 0.19 mmol) and the reaction was heated to reflux. The reaction was quenched after 6 h, followed by general work up, and column chromatography (15% EtOAc/Hex, R_f 0.25) provided **II-49j** as a solid (0.041 g, 81.0%). (*Diastereomeric ratio 2.3:1*) **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.72-7.50 (m, 1.26), 7.50-7.25 (m, 5.26), 7.25-6.98 (m, 6.06), 4.71-4.48 (m, 0.42), 4.32 (dd, *J* = 11.93, 4.36 Hz, 1.00), 3.89-3.54 (m, 13.78), 3.06-2.63 (m, 4.33), 2.63-2.31 (m, 4.05). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 187.5, 170.3, 160.7, 142.4, 136.4, 135.2, 134.9, 129.8, 128.9, 127.8, 125.0, 124.9, 54.9, 41.9,

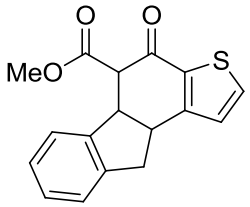
40.7, 37.2. **IR**: 3030(w), 2957(w), 2840(w), 1737(s), 1671(m), 1409(m), 1399(s) cm $^{-1}$. **HRMS (ESI)** M/Z+ Calc. 286.0664, Obs. 286.0674.



Methyl 4-oxo-7-phenyl-4,5,6,7-tetrahydrobenzofuran-5-carboxylate (II-49k). According to the general procedure, a solution containing $In(OTf)_3$ (12.4 mg, 0.23 µmol, 5 mol %) was added cyclopropane **II-48k** (0.12 g, 0.44 mmol). The reaction was quenched after 6 h, and column chromatography (20% EtOAc/Hex, R_f 0.25) provided **II-49k** as a solid (0.099 g, 82.5%). (*Diastereomeric ratio 1.2:1*) **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.35-7.20 (m, 5H), 7.11 (dd, *J* = 7.98, 1.57 Hz, 1H), 7.02 (dd, *J* = 7.78, 1.77 Hz, 1H), 4.44 (dd, *J* = 6.35, 5.92 Hz, 1H), 4.21 (dd, *J* = 10.39, 5.78 Hz, 1H), 3.67 (s, 3H), 3.66 (s, 3H), 3.64-3.49 (m, 1H), 2.84 (q, 1H), 2.65-2.47 (m, 1H), 2.41-2.23 (m, 1H)). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 188.4, 170.2, 166.7, 143.8, 139.1, 128.9, 127.7, 121.4, 106.8, 54.4, 52.5, 51.5, 41.1, 38.7, 36.0, 35.3. **IR**: 3121.1 (w), 2937.3(w), 1772.0 (s), 1729.7(s), 1684.0(m), 1605.2(w), 1583.6(m) cm^{-1}. **HRMS (ESI)** Calc. 270.0892, Obs. 270.0893.

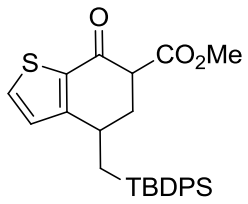


Methyl 4-methyl-7-oxo-4-phenyl-4,5,6,7-tetrahydrobenzo[b]thiophene-6-carboxylate (II-49l). According to the general procedure, to a solution containing $In(OTf)_3$ (7.06 mg, 0.125 μmol) was added cyclopropane **II-48l** (0.075 g, 0.25 mmol). The reaction was quenched after 4.5 h, and column chromatography (15% EtOAc/Hex, R_f 0.25) provided **II-49l** as a solid (0.053 g, 71.0 %). (*Diastereomeric ratio 2:1*) **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.91 (dd, *J* = 3.86, 1.09 Hz, 1H), 7.84-7.75 (m, 1H), 7.73-7.67 (m, 1H), 7.44-7.25 (m, 2H), 7.21-7.09 (m, 1H), 7.10-6.93 (m, 1H), 4.32 (dd, *J* = 9.84, 9.00 Hz, 1H), 3.76-3.67 (s, 3H), 3.36-3.06 (m, 1H), 2.88-2.38 (m, 1H), 1.83-1.79 (s, 3H). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 187.5, 170.4, 157.5, 144.6, 135.5, 128.6, 128.3, 127.7, 126.9, 126.8, 126.3, 126.2, 125.0, 52.3, 51.8, 43.5, 42.1, 29.5. **IR**: 3002 (w), 2951(w), 2923(w), 1721(s), 1682(s), 1661(s), 1515(w), 1444(s) 1410(m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 300.0820, Obs. 300.0830.

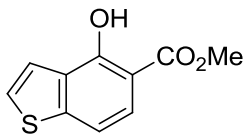


Methyl 4-oxo-5,5a,10,10a-tetrahydro-4H-fluoreno[2,1-b]thiophene-5-carboxylate (II-49m). According to the general procedure, a solution containing $In(OTf)_3$ (4.71 mg, 8.38 μmol) was added cyclopropane **II-48m** (0.050 g, 0.17 mmol). The reaction was quenched after 6 hours, and column chromatography (15% EtOAc/Hex, R_f 0.25) provided **II-49m** as a solid (0.043 g, 87.0 %). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.80 (td, *J* = 3.86, 1.18, 1.18 Hz, 1H), 7.75-7.62 (m, 1H), 7.50 (td, *J* = 8.63, 3.74, 3.74 Hz, 1H), 7.45-7.31 (m, 1H), 7.31-7.05 (m, 1H), 6.99-6.81 (m, 1H), 4.10 (s, 1H), 3.92-3.62 (m, 1H), 3.62-3.41 (m, 1H). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 185.6, 168.7, 143.9, 142.3, 139.8,

135.1, 133.3, 132.6, 128.4, 126.3, 125.0, 123.6, 121.1, 57.7, 52.8, 40.1. **IR**: 2930 (m), 2847(w), 1737(s), 1664(s), 1959(s), 1595(w), 1413(m), 1254(s), 1207(s), 1147(s), 1087(s) cm $^{-1}$. **HRMS (ESI)** M/Z+ Calc. 298.0670, Obs. 298.0697.

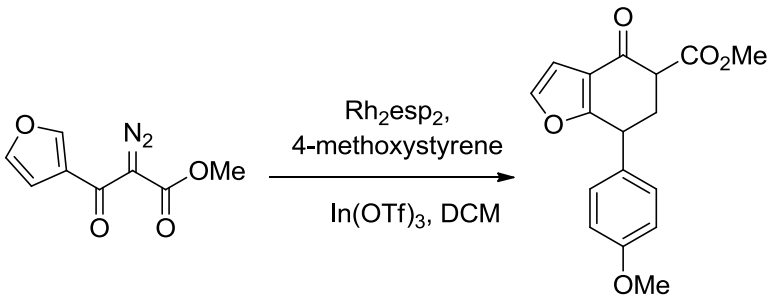


Methyl 4-((tert-butyldiphenylsilyl)methyl)-7-oxo-4,5,6,7-tetrahydrobenzo[b] thiophene-6-carboxylate (II-49n). According to the general procedure, a solution containing $In(OTf)_3$ (12.1 mg, 0.21 µmol, 30 mol %) was added cyclopropane **II-48n** (0.10 g, 0.429 mmol). The reaction was quenched after 6 h, and column chromatography (20% EtOAc/Hex, R_f 0.25) provided **II-49n** as a solid (0.071 g, 71.0 %). (*Diastereomeric ratio 2.4:1*) **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.76-7.62 (m, 8.34), 7.60-7.53 (d, *J* = 5.05 Hz, 2.15), 7.48-7.29 (m, 14), 7.10-7.00 (dd, *J* = 8.49, 5.31 Hz, 1.69), 6.79 (d, *J* = 5.02 Hz, 0.65), 3.70-3.66 (d, *J* = 4.46 Hz, 2.23), 3.64-3.58 (m,1.09), 3.60-3.54(s, 2.46), 3.31-3.00 (m, 2.92), 2.39-1.98 (m, 1.39), 2.18-1.76(m, 4.81), 1.72-1.36 (m, 5.62), 1.15-0.99 (m, 18.39). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 187.7, 186.6, 169.9, 159.1, 136.1, 136.0, 135.9, 135.9, 134.9, 129.6, 129.5, 129.4, 128.0, 127.9, 127.8, 127.7, 127.6, 52.2, 51.1, 30.6, 27.8, 27.7, 18.3. **IR**: 2926.6, 2854.9, 1741.5, 1677.6, 1457.6, 1426.6, 1274.9, 1260.1 cm^{-1}. **HRMS (ESI)** Calc. 462.1719 Obs. 462.1681.



Methyl 4-hydroxybenzofuran-5-carboxylate (II-49o). According to the general procedure, a solution containing $In(OTf)_3$ (11.8 mg, 0.21 μmol) in CH_2Cl_2 was added cyclopropane **II-48p** (0.10 g, 0.419 mmol). The reaction was quenched after 24 h, and column chromatography (15% EtOAc/Hex, R_f 0.25) provides the product **II-49o** as a white solid (0.081 g, 81.0%). All data matches literature.

2.8.2.6.Tandem Cyclopropanation-Formal Homo-Nazarov Cyclization



To a flame dried flask containing Rh_2esp_2 (6.00 mg, 7.93 μmol) and $In(OTf)_3$ (1.01 mg, 1.79 μmol) in DCM (2 mL) was added 4-methoxystyrene (0.106 g, 0.793 mmol) at 0 °C. After 5 minutes, a solution of α-diazo ester **II-51d** (0.200 g, 1.03 mmol) in DCM (2mL) was added to the flask. The ice bath was removed after 10 minutes and the reaction was allowed to warm up to RT. The reaction was quenched with water after 12 hours, extracted with DCM (3x), dried with Na_2SO_4, and column chromatography (10% EtOAc/hexane, R_f 0.15) afforded **II-49d** as a solid (0.060 g, 56.6%).

2.9. REFERENCES

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CHAPTER 3

SYNTHESIS OF HYDROPYRIDO[1,2-*a*]INDOLE-6(7*H*)-ONES VIA AN INDIUM(III)-CATALYZED TANDEM CYCLOPROPANE RING-OPENING/FRIEDEL-CRAFTS ALKYLATION SEQUENCE[‡‡]

3.1. HYDROPYRIDO[1,2-*a*]INDOLES IN NATURE

A common motif present in an astonishing variety of natural products endowed with potent and multiform biological activities is an indole nucleus annulated to carbo- or heterocyclic ring(s).[1-6] A large number of indole compounds are at the forefront as pharmacologically-active lead compounds for drug discovery and development processes. At present, more than 2000 indole alkaloid natural products have been characterized, which encompasses simple and more complex functionalized indole derivatives.[7] Among [*a*]-annelated systems, the hydropyrido[1,2-*a*]indole skeleton (**III-1**) and, more specifically, its C(6)-oxidized cogeners (**III-2**) are key structural motifs that appear in the core structures of an impressive number of naturally-occurring indole alkaloids and pharmaceutically relevant compounds (Figure 3.1).

[‡‡]This work was performed in collaboration with Marchello A. Cavitt, a fellow graduate student and Paul Grzybowski, an undergraduate student in the France research group.

In 1818, Pelletier and Caventou reported the first isolation of the bioactive pentacyclic alkaloid strychnine (**III-3**) from S*trychnos ignatii*.[8] *Vinca* alkaloids comprise a large number of biologically active, naturally-occurring bases isolated from several plants of the *Vinca* species.[9] For example, vincamine (**III-4**) possesses strong antihypertensive and sedative properties.[10] Vinpocetine (**III-5**)[11] exhibits strong cerebrovascular, antihypoxic, antiamnesic, antiischemic, and cytoprotective effects.[12,13] (-)-Eburnamonine (**III-6**) and (±)-vindeburnol (**III-7**) shows strong vasodilation activity.[14] The structurally related *tacaman* alkaloids represented by tacamine (**III-8**), and tacamonine (**III-9**) show potential hypotensive and cerebral vasodilation effects.[15,14c] Indole alkaloids mersicarpine (**III-11**),[16] leuconoxine (**III-14**),[17] and arboloscine (**III-13**)[18] are isolated from the plants of genus *Kopsia*. Novel pentacyclic indole alkaloids, tronocarpine (**III-10**)[19] and dippinine (**III-12**)[20] are isolated from the plants of the genus *Tabernaemontana.* (-)-Goniomitine (**III-15**) isolated from the root bark of *Gonioma Malagasy,* has shown strong antitumor activity against several types of cancer cell lines.[21]

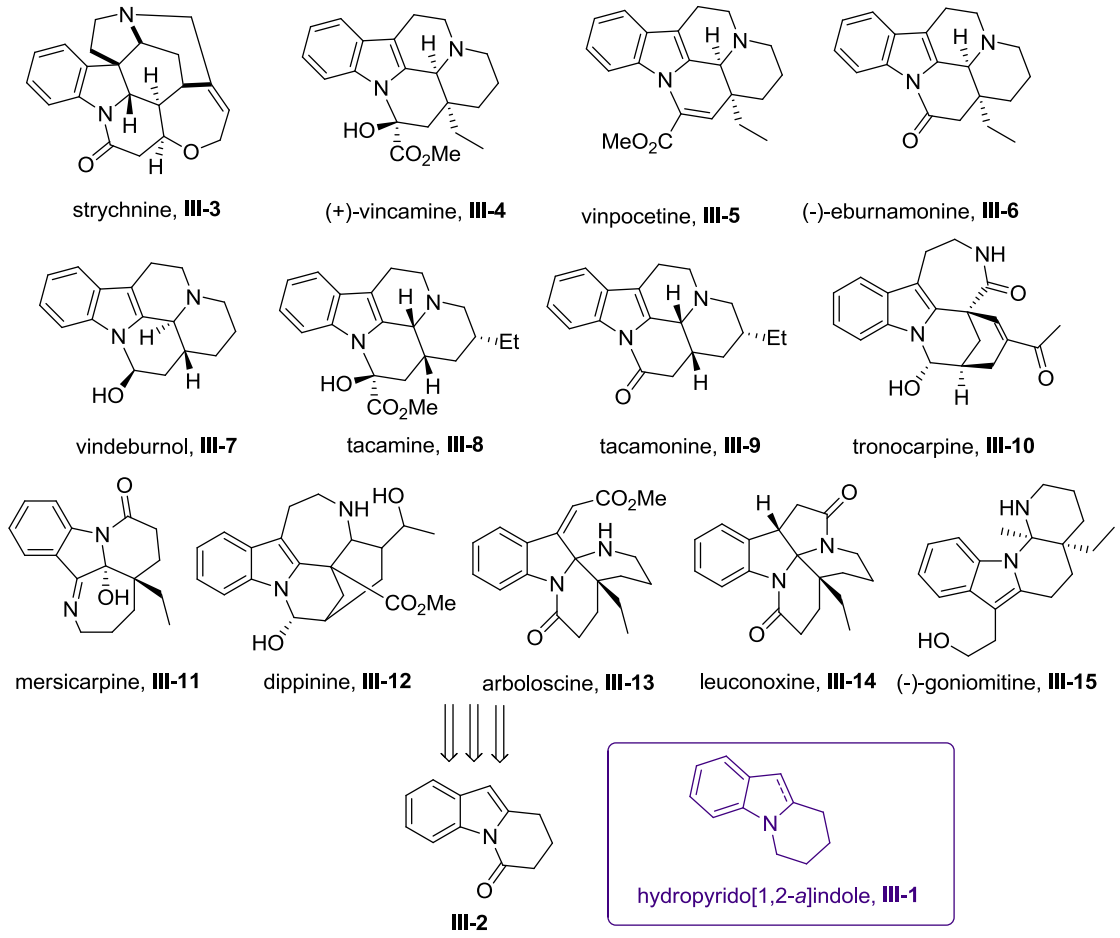


Figure 3.1. Representative Hydropyrido[1,2-*a*]indole Containing Natural Products

3.2. SYNTHESIS OF FUNCTIONALIZED HYDROPYRIDO[1,2-*a*]INDOLES

Owing to hydropyrido[1,2-*a*]indoles existence in a wide variety of natural products and molecules with interesting biological properties, extensive efforts have been devoted towards the synthesis of functionalized annulated indoles. The majority of synthetic approaches to construct these skeletons begin with an indole framework and the piperidine ring was installed through transition metal-catalyzed C-C bond formation,[22] intra/intermolecular condensations,[23] radical cyclizations,[24] nucleophilic substitutions,[25] acid-induced cyclizations,[26] cycloadditions,[27] Pauson-Khand reactions,[28] and domino reactions.[29] Due to the sheer number of strategies reported, the following section provides

a brief overview of some representative approaches to hydropyrido[1,2-*a*]indoles with an example given for each synthetic route.

3.2.1. TRANSITION METAL-CATALYZED C-C BOND FORMATION

In 2007, the Zhang group elegantly presented a Pt-catalyzed synthesis of substituted indoles fused to cyclic ketones (Figure 3.2).[22b] *N*-(2-alkynylphenyl)lactams **III-16** were heated to reflux in 1,2-dichloroethane in the presence of catalytic amounts of $PtCl_4$ under an atmosphere of O_2 to furnish annulated indole products **III-17**. This reaction proceeds through an intramolecular insertion at one end of the C-C triple bond into the lactam amide bond with concurrent 1,2-acyl migration of the substituent on the triple bond. When reactions were performed using either $PtCl_2$ or under nitrogen atmosphere, increased reaction time was observed. Studies indicated that the reaction time was shortened upon the use of O_2. The Zhang group also demonstrated that the reaction works well when alkyl, cycloalkanes, aryl, and alkenyl groups were present at the alkyne terminus. The reaction did not show any electronic effect from the substituent of the benzene ring on the product outcome. This chemistry was also extended to 4- and 6-membered lactams.

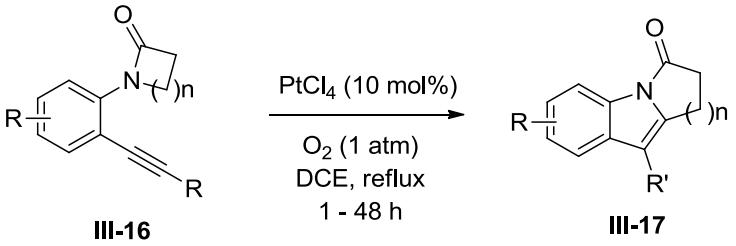


Figure 3.2. $PtCl_4$ Catalyzed Cycloisomerization of *N*-(2-Alkynylphenyl)lactams

3.2.2. INTRA/INTERMOLECULAR CONDENSATIONS

In 1998, Skibo *et al.* designed a system that could form a cyclopropyl quinone methide from a pyrrolo[1,2-*a*]-fused system upon reduction of the quinone. In the continuation of their effort, the Skibo group utilized pyrido[1,2-*a*]-fused systems to develop cyclopropyl quinone methide reductive alkylating agents.[23b] The required annulated pyrido ring products **III-19** were synthesized by condensation of indole **III-18** with γ-butyrolactone followed by a dehydrative cyclization using hot polyphosphoric acid (Figure 3.3).

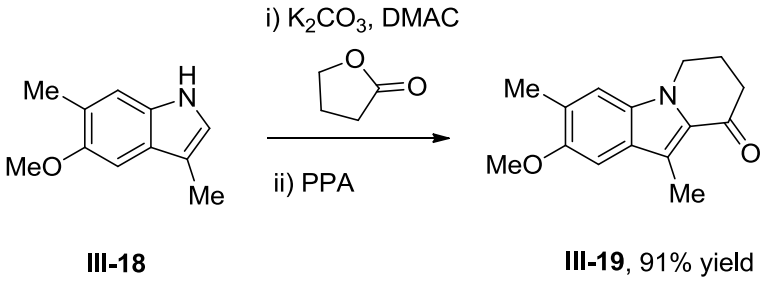


Figure 3.3. Pyrido[1,2-*a*]indole Synthesis via an Intermolecular Condensation Reaction

3.2.3 RADICAL CYCLIZATION APPROACH

A more common approach in the synthesis of hydropyrido[1,2-*a*]indole compounds is the construction of the 6-membered ring via a radical cyclization. More recently, the Kerr group demonstrated the utility of this route to generate 1,2-annulated indole/pyrroles.[24c] A variety of *N*-acylated or alkylated indoles/pyrroles were subjected to oxidative cyclization with excess $Mn(OAc)_3$ in methanol to furnish products **III-21** in high yields (Figure 3.4). However, the substrate derived from indole-3-carbaldehyde did not cyclize under the optimized conditions. The reaction is postulated to proceed through the oxidation of a malonic enolate derived from **III-20** to yield a malonic radical.

Cyclization onto the 2-position of an indole or pyrrole yields a resonance stabilized radical which undergoes further oxidation to carbonium ion. Aromatization via proton loss gives the product **III-21**. Further studies showed that indolines can also be employed as substrate to form 1,2-annulated products in a one-pot fashion. To showcase the application of the method, the tetracyclic core of tronocarpine **III-22** was synthesized. In 2008, this sequence was first applied in the successful total synthesis of mersicarpine.[24a]

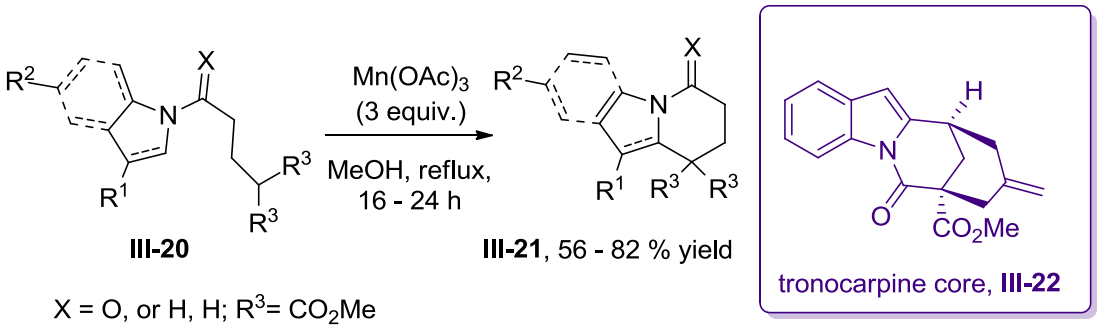


Figure 3.4. Radical Cyclization Route to Pyrido[1,2-*a*]indole Synthesis

3.2.4. NUCLEOPHILIC SUBSTITUTION APPROACH

The Okda group reported the application of nucleophilic substitution approach towards the synthesis of (+)-dihydroeburnamenine **III-25** and (-)-epidihydroeburnamenine **III-26** natural products in 2004 (Figure 3.5).[25b] When mesylate **III-23** was treated with NaOH in THF, it readily formed *N*-alkylated pentacyclic product **III-24** in 88% yield. Reduction of lactam **III-24** was then performed with $LiAlH_4$ in THF at reflux to provide **III-25 i**n 91% yield. Similarly, reduction of another isomer of **III-24** using an excess amount of $NaBH_4$/TFA in dioxane afforded **III-26** in 87% yield.

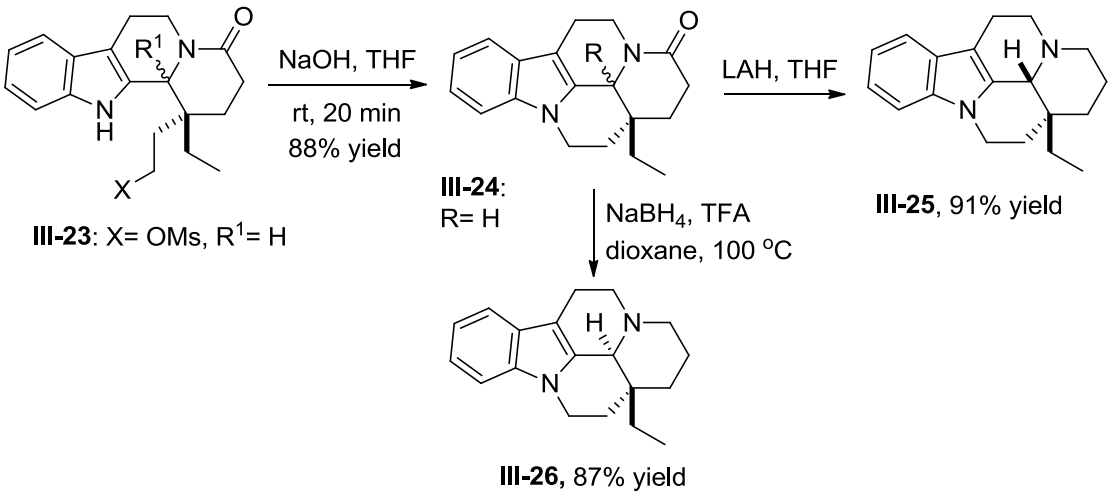


Figure 3.5. Synthesis of Pyrido[1,2-*a*]indoles via a Nucleophilic Substitution Route

3.2.5. ACID-INDUCED CYCLIZATION ROUTES

In their synthetic studies towards the discovery of novel protein kinase Cβ (PKCβ)- selective inhibitors possessing oral bioavailability as a potential candidate in the treatment of diabetes mellitus, the Inaba group designed and synthesized pyrido[1,2-*a*]indole derivatives.[26a] An intramolecular Pictet-Spengler cyclization of *N*-alkylated indole **III-27** in the presence of TFA allowed the formation of 1,2-annulated indole derivative **III-28** (Figure 3.6). Ultimately, it was used in the synthesis of conformationally restricted 3-anilino-4-(3-indolyl)maleimide derivatives **III-29**.

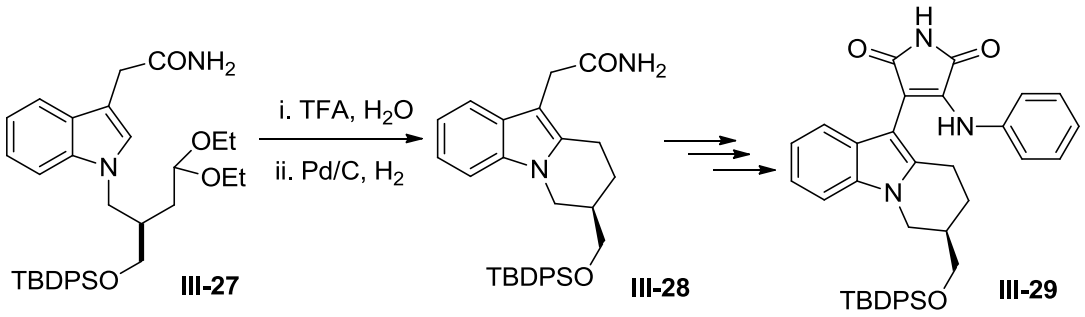


Figure 3.6. Synthesis of Pyrido[1,2-*a*]indoles by Acid-Induced Cyclizations

3.2.6. CYCLOADDITIONS APPROACHES

The Bodwell group developed a novel transannular inverse electron demand Diels-Alder (IEDDA) reaction that utilizes small cyclophanes as key intermediates to natural products.[27c, 30] When indolophane **III-30** was heated with *N*,*N*-dimethylaniline it formed a pentacyclic pyrido[1,2-*a*]indole product **III-32**, which appears to be well suited as a precursor to a variety of indole alkaloids, such as strychnine. The reaction presumably proceeds via an IEDDA reaction to give adduct **III-31**, followed by expulsion of N_2 in a retro Diels-Alder fashion (Figure 3.7). Furthermore Bodwell disclosed a concise formal synthesis of (±)-strychnine with an overall yield of 2.6% over twelve steps. Thus, making it the shortest synthetic route reported to strychnine.

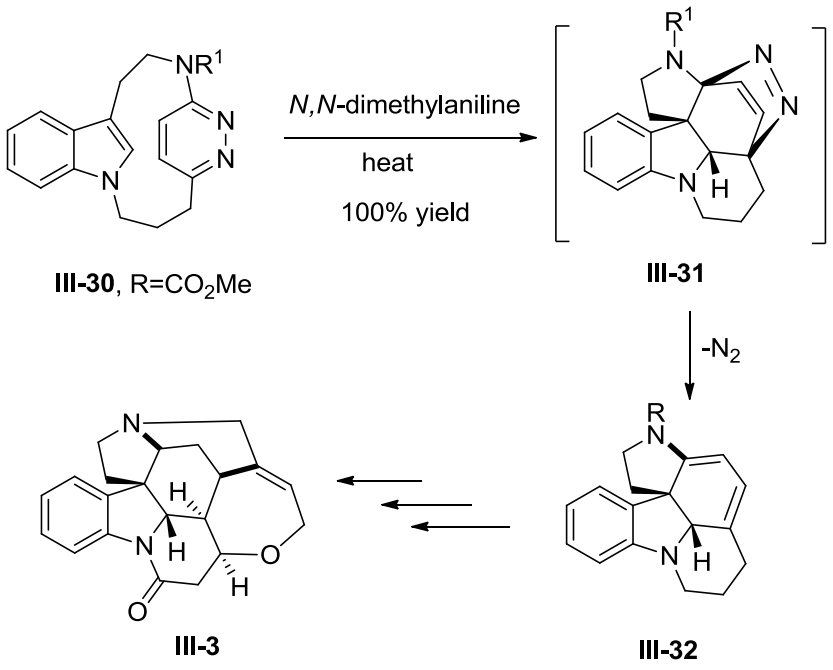


Figure 3.7. Cycloaddition Reaction to Access Pyrido[1,2-*a*]indole Skeletons

3.2.7. PAUSON-KHAND REACTION APPROACH

The Pauson-Khand reaction is one of the least explored strategies in indole chemistry. More specifically, it remains an uncommon route in the synthesis of the pyrido[1,2-*a*]indole framework. In 2004, the Pe´rez-Castells group demonstrated the utility of this reaction towards the construction of tetracyclic compounds fused at positions 1 and2 (**III-35**); 2 and 3 (**III-34**); and 3,3a and 4 (**III-36**) of the indole nucleus (Figure 3.8).[28] Indoles bearing an alkenyl and alkynyl moiety **III-37** was heated in the presence of $Co_2(CO)_8$/TMANO to furnish the 1,2-annulated indole product in high yield. The group also showed the scope of the reaction by screening indoles bearing a wide variety of alkenyl and alkynyl moieties to provide tetracyclic cyclopentenone products in moderate to high yield. Further studies showed that that the starting materials with bulky

groups such as TBDMS or Phth, a single diastereomer was observed. The bulkier group is found to be on the same side as the hydrogen at the ring junction **(III-38)**.

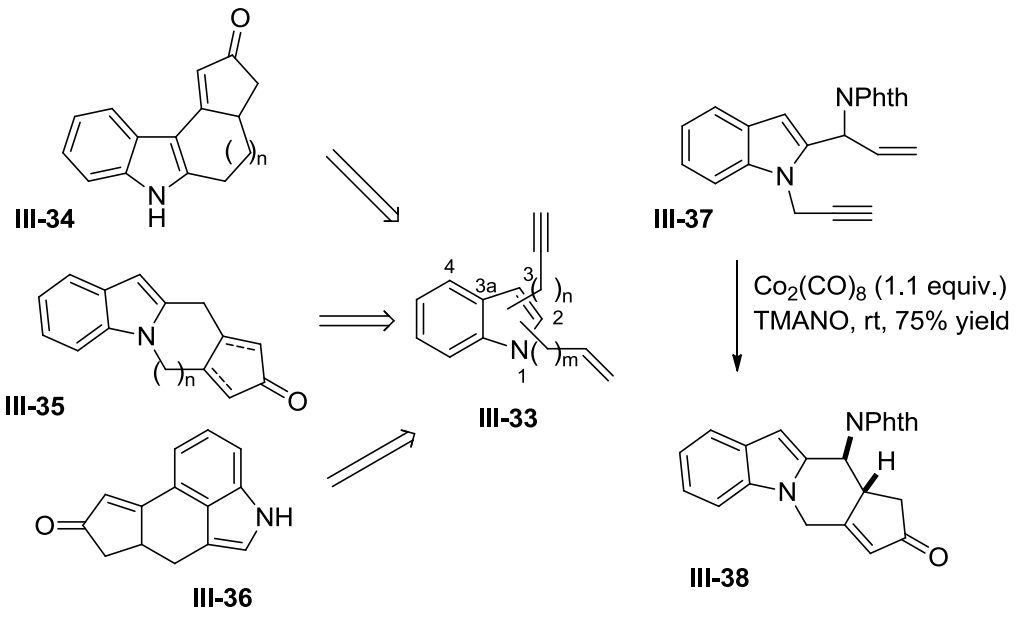


Figure 3.8. Synthesis of Pyrido[1,2-*a*]indoles by Pauson-Khand Reactions

3.2.8. DOMINO REACTION APPROACH

Domino reactions are considered to be one of the most valuable methods for an efficient construction of complex skeletons in contemporary organic synthesis.[31] Wang *et al.* reported NHC-catalyzed domino reactions of 1,1-diactivated FCPs with salicylaldehyde to generate coumarin skeletons.[32] In a continuation of their studies, the Wang group developed a domino ring-opening/redoxamidation/cyclization reaction of readily available formylcyclopropane 1,1-diesters **III-40** with 2-chloro-1*H*-indole-3-carboaldehydes **III-39** to generate hydropyrido[1,2-*a*]indoles **III-41** (Figure 3.9).[29] Further studies on the reaction scope showed that substituent on the phenyl ring of the indole significantly affect the reaction yield and conversions. Substrates with an EWG showed low to moderate yields and conversions. Even 2-chloro-1*H*-benzimidazole was

found to be suitable substrate for the reaction. Finally, the utility of this efficient protocol was established by synthesizing the tetracyclic unit of tronocarpine (**III-42**).

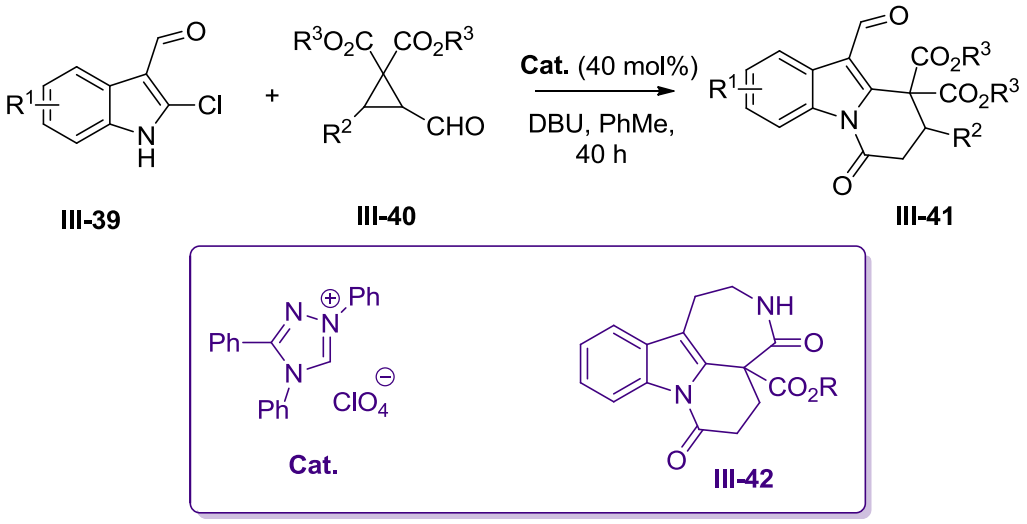


Figure 3.9. Domino Reaction in the Synthesis of Pyrido[1,2-*a*]indoles

Unfortunately, many of these strategies usually provide products in modest yields, requires high catalyst loadings, and involve either extensive multi-step sequences to construct the 1,2-annulated indole ring system or do not allow for a large range of functionality to be accessed. Therefore, the discovery of a more general and efficient method for the facile construction of this polycyclic core remains a formidable goal for organic chemists. In the following section, the France Lab efforts directed towards the development of an efficient methodology for the synthesis of densely functionalized hydropyrido[1,2-*a*]indole skeletons will be discussed.

3.3. THE DEVELOPMENT OF INDIUM(III)-CATALYZED TANDEM CYCLOPROPANE RING-OPENING/FRIEDEL-CRAFTS ALKYLATION

3.3.1. PRIOR CONTRIBUTIONS MADE BY THE FRANCE GROUP

The previous work from the France group demonstrated that the formal homo-Nazarov cyclization of alkenyl and heteroaryl cyclopropyl ketones could be significantly facilitated if the cyclopropanes were functionalized to bear an additional electron acceptor (such as an ester) in the α-position (Figure 3.10).[33]

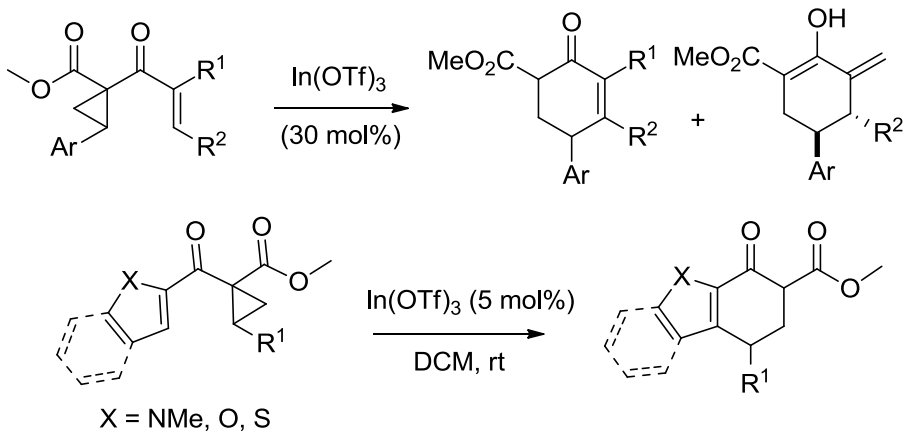


Figure 3.10. Formal Homo-Nazarov Cyclization Developed in the France Lab

The successful synthesis of heteroaromatic-ring fused cyclohexanone via the formal homo-Nazarov cyclization of heteroaryl cyclopropyl ketones under mild reaction conditions suggested that by employing these donor-acceptor-acceptor (D-A-A) cyclopropanes with *N*-acylated indoles as reactive π-systems, would easily generate hydropyrido[1,2-*a*]indole compounds.

3.3.2. SUBSTRATE SYNTHESIS

In order to test our hypothesis, cyclopropane precursors **III-45** were prepared in three steps according to Figure 3.11. *N*-Acylation of an indole with commercially-available methyl malonyl chloride afforded the β-amidoester compounds **III-43**. Next, diazo transfer provided α-diazoester **III-44**. Lastly, cyclopropanation[34] with Rh_2esp_2 (bis[rhodium(α,α,α',α'-tetramethyl-1,3-benzenedipropionic acid)]) in the presence of a requisite alkene provided the desired methyl 1-(1*H*-indole-carbonyl)-1-cyclopropanecarboxylates **III-45** with a overall yields (over three steps) up to 70%.

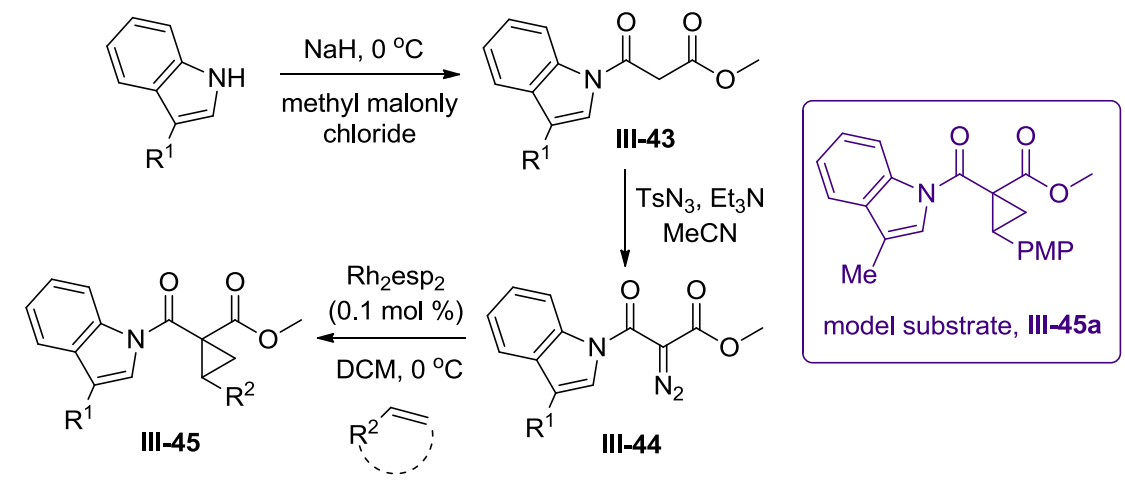


Figure 3.11. *N*-Substituted Indolyl Cyclopropanes Synthesis

Given the 3-methyl-1*H*-indole's ability to act as a good nucleophile and the cation stabilizing ability of 4-methoxyphenyl, an *N*-substituted indolyl cyclopropane bearing a 4-methoxyphenyl group was chosen as the model substrate for preliminary investigation. The *N*-substituted indolyl cyclopropane **III-45a** was synthesized.

3.3.3. PROOF OF CONCEPT/REACTION OPTIMIZATION

With a diverse set of substrates in hand, it was necessary to find conditions that allowed for the successful cyclization of the methyl 1-(1*H*-indole-carbonyl)-1-cyclopropanecarboxylates. Based on our recent success with $In(OTf)_3$ as an effective catalyst in the formal homo-Nazarov cyclization reaction of alkenyl and heteroaryl cyclopropyl ketones, we utilized $In(OTf)_3$. The model substrate **III-45a** was subjected to 30 mol% $In(OTf)_3$ in dichloromethane at room temperature. We were delighted to see a quantitative conversion to the desired hydropyrido[1,2-*a*]indole product **III-46a** (Figure 3.12).

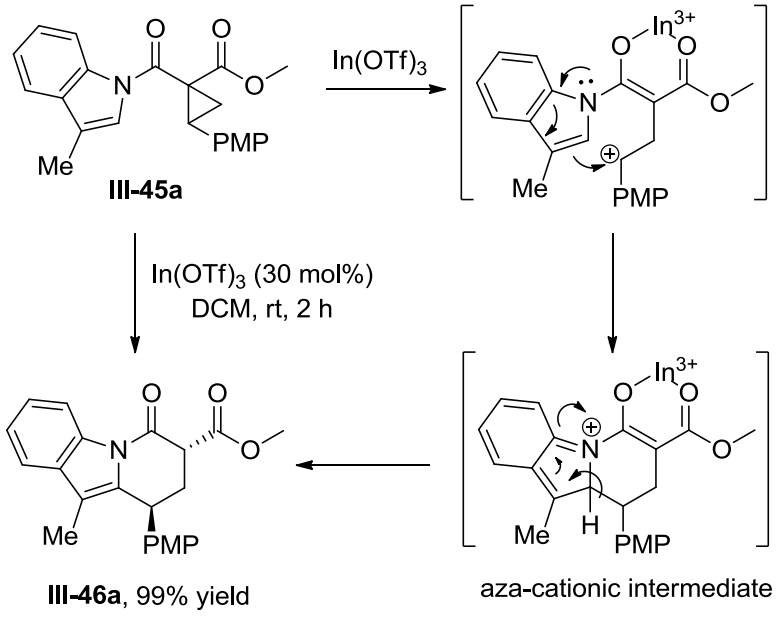
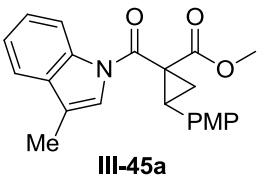
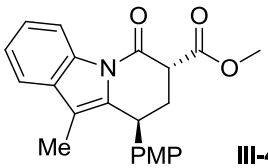
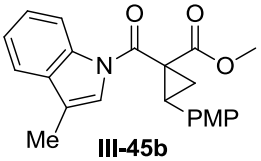
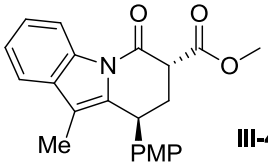
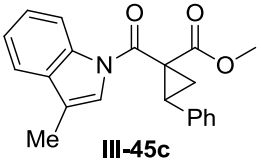
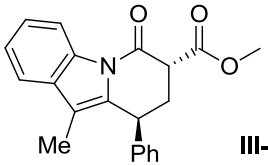
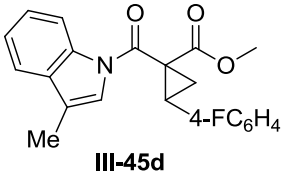
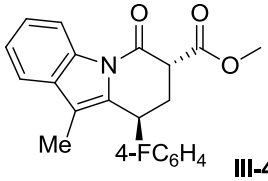
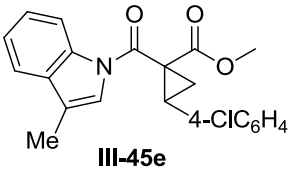
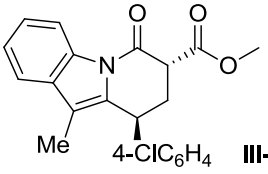
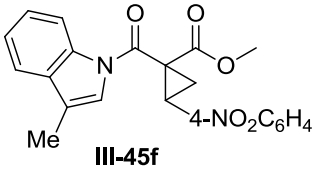
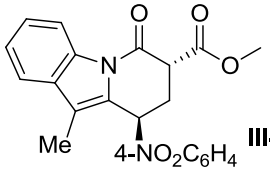
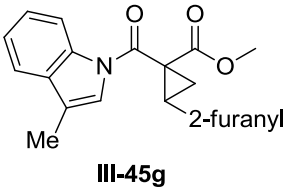
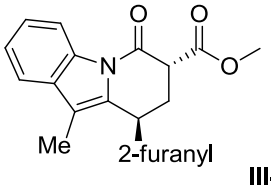


Figure 3.12. Proof of Concept: In(III)-Catalyzed Tandem Cyclopropane Ring-Opening/ Friedel-Crafts Alkylation Sequence

3.3.4. AN EXAMININATION OF THE REACTION SCOPE AND LIMITATIONS

With promising preliminary reaction conditions identified, the effects of various aryl/heteroaryl substituents as donor groups on the cyclopropane were examined. As mentioned on previous page, cyclopropane **III-45a** rapidly cyclized to afford the product **III-46a** in almost quantitative yield with 2.6:1 *trans:cis dr* (Table 3.1, entry 1). Likewise, 2-methoxy phenyl cyclopropane **III-45b** provided product **III-46b** in 95% yield with 3.2:1 *dr* (Table 3.1, entry 2). Thus, electron-donating groups such as methoxy group in both *ortho*- and *para*-position favored the reaction, providing the corresponding products in excellent yields. Next, to probe the electronic effects of the *para*-substituted aromatic cyclopropane on the reaction outcome, cyclopropanes with the phenyl, 4-fluorophenyl, 4-chlorophenyl and the 4-nitrophenyl as the EWG donor group were synthesized. Disappointingly, when the phenyl derivative **III-45c** was subjected to the reaction conditions, the reaction failed to produce any of the desired product **III-46c**. Instead, only starting material was recovered even after long reaction times (>24 h). It was thought that the use of higher temperature may prove more successful. Therefore, the substrate **III-45c** was heated to reflux in 1,2-dichloroethane. As anticipated, it cyclized to provide corresponding product **III-46c** in 52% yield with 2.6:1 *dr* (Table 3.1, entry 3). Similarly, substrates with electron-withdrawing groups such as F, Cl, and NO_2 groups on the *para*-position of the phenyl ring **III-45(d-f)** did not provide any of the desired products at room temperature. However, upon subjecting the substrate to reflux in 1,2-DCE, the cyclized products were observed. The 4-fluorophenyl and 4-chlorophenyl derivatives furnished cyclized products **III-46d** and **III-46e** in 48% and 50% yield, respectively (Table 3.1, entries 4 and 5).

Table 3.1. Effect of Aryl/Heteroaryl Substituted Cyclopropanes on the Reaction[a]

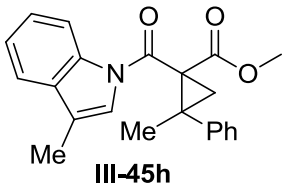
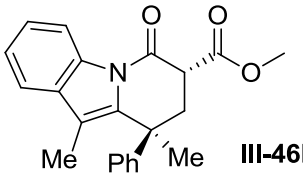
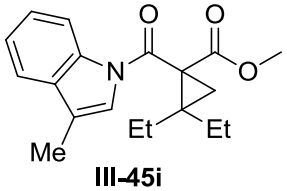
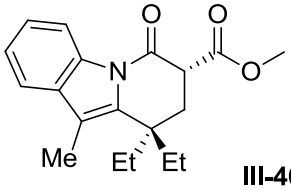
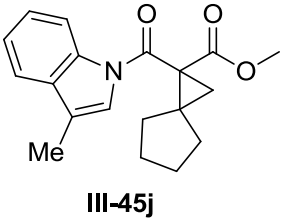
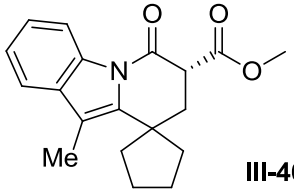
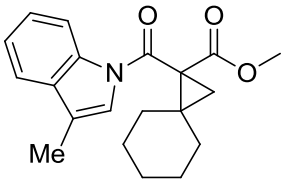
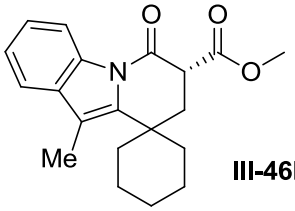
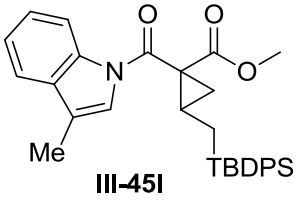
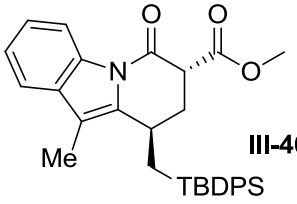
entry	substrate	product	time (h)	yield[b] (%)	*dr*[c] *(trans/cis)*
1	 **III-45a**	 **III-46a**	2.0	99	2.6:1
2	 **III-45b**	 **III-46b**	3.0	95	3.2:1
3[d]	 **III-45c**	 **III-46c**	8.0	52	2.6:1
4[d]	 **III-45d**	 **III-46d**	8.0	48	2.6:1
5[d]	 **III-45e**	 **III-46e**	12.0	50	1.9:1
6[d]	 **III-45f**	 **III-46f**	20.0	*trace*	---
7	 **III-45g**	 **III-46g**	2.0	99	4.5:1

[a]Reactions run with 1 equiv. substrate and 30 mol% $In(OTf)_3$ in DCM at 25 °C. [b]Isolated yields after column chromatography. [c]Diastereoselectivities determined from ^1H NMR of the crude reaction mixture and represent *trans:cis* diastereomeric ratios. [d]Reaction performed in 1,2-DCE at 80°C.

This result is noteworthy as the aromatic halogen may serve as a chemical handle for further synthetic functionalization. The 4-nitro derivative **III-45f** only afforded trace amounts of the desired product **III-45f** as indicated by crude ^{1}H NMR (Table 3.1, entry 6). Consideration of the electronics of the reaction suggested that there would be an increased destabilizing effect on the benzylic carbocation formed upon cyclopropane ring opening in the transition state (Figure 3.12). This effect is more pronounced as the substituents are varied from the electron-donating 4-methoxy group to the electron-withdrawing 4-nitro group and thus contributing to the observed failure of the reaction. These observations correlate well with known Hammett substituent values for benzylic cations.[35] Similar reactivity was observed when a heteroaromatic group was employed as the donor substituent. For example, with furan as the donor group, cyclized product **III-46g** is readily obtained in 99% yield with 4.5:1 *dr* (Table 3.1, entry 7). This result is notable in that furyl donor groups of this type have previously been shown to be prone to polymerization.[36]

Next, the reaction scope of was examined using cyclopropanes with another cation stabilizing donor substituent. The geminally disubstituted cyclopropane substrate **III-45h** was subjected to the standard reaction conditions. As anticipated, it resulted in a dramatic accelerating effect. This effect can be seen in that **III-45h** readily cyclizes at room temperature to afford **III-46h** in excellent yield (94%) with 1.1:1 *dr* (Table 3.2, entry 1), whereas **III-45c** does not cyclize at room temperature. The enhanced reactivity of **III-45h** is presumably attributed to faster ring-opening of the cyclopropane due to a release of steric ring strain and the formation of the more stable 3° benzylic carbocation. This result is noteworthy because a quaternary stereocenter is generated.

Table 3.2. Effect of Disubstituted/2-Silylmethylsubstituted Cyclopropanes[a]

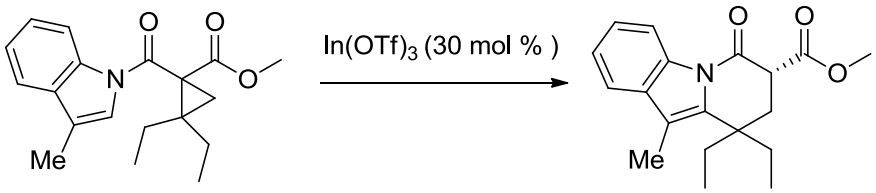
entry	substrate	product	time (h)	yield[b] (%)	*dr*[c] *(trans/cis)*
1	 **III-45h**	 **III-46h**	2.0	94	1.1:1[e]
2[d]	 **III-45i**	 **III-46i**	6.0	85	----
3[d]	 **III-45j**	 **III-46j**	6.0	88	----
4[d]	 **III-45k**	 **III-46k**	6.0	79	----
5[d]	 **III-45l**	 **III-46l**	16.0	82	----*f*

[a] Reactions run with 1 equiv. substrate and 30 mol% $In(OTf)_3$ in DCM at 25 °C. [b] Isolated yields after column chromatography. [c] Diastereoselectivities determined from ^1H NMR of the crude reaction mixture and represent *trans:cis* diastereomeric ratios. [d] Reaction performed in 1,2-DCE at 80°C. [e] Relative configurational assignment not determined. [f] Only one diastereomer visible by ^1H NMR.

The increased reaction rate and excellent yield observed in the case of **III-45h** substrate indicated that the reaction might be proceeding through a more stable 3° benzylic carbocationic intermediate. This interesting result prompted us to investigate the use of geminal disubstituted alkyl groups as a donor on the cyclopropanes. Previous literature findings showed that the tertiary carbocations are very close in energy to benzylic carbocations.[37] Thus, the cyclopropane ring-opening should be favored to generate a more stable 3° carbocation, providing the corresponding hydropyrido[1,2-*a*]indole derivatives. To confirm this hypothesis, substrate **III-45i** (derived from 3-methylene pentane) was chosen as a substrate of choice for initial testing because it has an easily identifiable ^{1}H NMR spectra and would simplify interpretation of the cyclized product in the spectrum. Disappointingly, using identical reaction conditions as before, the geminal diethyl substituted cyclopropane did not undergo any appreciable cyclization (Table 3.3, entry 1). As it was our intention to develop the method to be applicable to dialkyl substituted cyclopropanes, further optimization was undertaken varying the temperature, order of addition of the reagent, and solvent. The optimization study began by examining the reaction at slightly higher temperature. Interestingly, no reaction occurred when substrate **III-45i** was reacted in dichloromethane at reflux (Table 3.3, entry 2). The next stage of the optimization process was to investigate the order and temperature at which the reagents were combined. When the cyclopropane was added to a refluxing solution of the Lewis acid in dichloromethane, disappointingly cyclopropane ring-opening was still disfavored (Figure 3.3 entry 3). Next, the substrate was treated with 30 mol % $In(OTf)_3$ in 1,2-dichloroethane at room temperature and gradually heated to reflux (Figure 3.3, entry 4). However, this condition also proved unsuccessful to

furnish any cyclized product even after long reaction times (>24 h). Later when the reaction was repeated by combining the Lewis acid and 1,2-DCE at room temperature and then heating to reflux for 5 min. The cyclopropane substrate was then added rapidly in one portion. The reaction progress was monitored by TLC. Gratifyingly, a complete disappearance of the starting material after 6 h was observed, providing product in 85 % yield (Figure 3.3, entry 5). The results of the screening reactions indicated that the Lewis acid and cyclopropane could not be mixed together at room temperature and then heated to reflux. The reason for the reaction outcome on the temperature dependent order of addition is unclear at this moment.

Table 3.3. Summary of the Conditions Tested on Substrate **III-45i**



III-45i **III-46i**

entry	reaction conditions	% yield
1[a]	DCM, rt, >12 h	NR
2[a]	DCM, reflux, >12 h	NR
3[b]	DCM, reflux, > 12 h	NR
4[a]	1,2 -DCE, reflux, >12	NR
5[b]	1,2 -DCE, reflux, >12	85

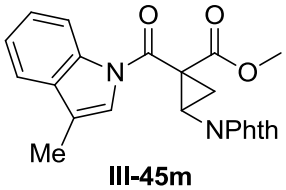
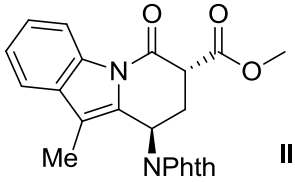
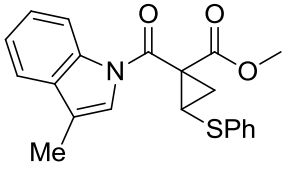
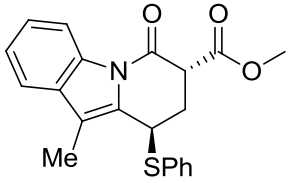
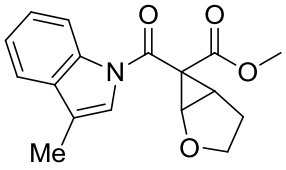
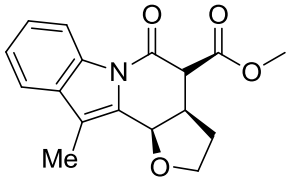
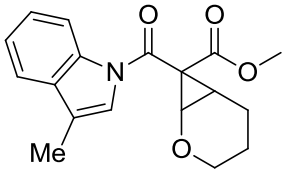
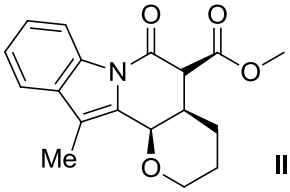
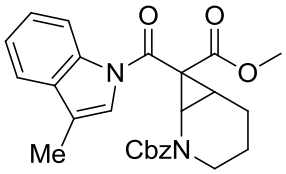
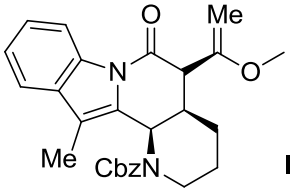
[a] Method A: cyclopropane and LA combined at rt; [b] Method B: cyclopropane was added to refluxing solution of LA in solvent

Having determined that addition of cyclopropane to a refluxing solution of the Lewis acid in DCE improved the yield, substrate **III-45j** (derived from methylene cyclopentane) and **III-45k** (derived from methylene cyclohexane) was subjected to this modified protocol to afford their respective hydropyrido[1,2-*a*]indole products **III-45j**, and **III-45k** in 88% and 79% yield (Table 3.2, entries 3 and 4). These results are particularly notable for several reasons: (1) spirocyclic compounds (as in **III-45j** and **III-45k**) can be readily accessed from an appropriate 1,1-disubstituted alkene; (2) the successful use of alkyl groups as donors were limited to Tsuge's seminal report;[38] and (3) a number of hydropyrido[1,2-*a*]indole natural products have gem-dialkyl substituents at C(9).

Inspired by Yadav and co-workers recent work on the development of formal homo-Nazarov cyclization of heteroaryl 2-silylmethyl-substituted cyclopropanes to generate 2,3-heteroaromatic ring-fused cyclohexanones,[39] scope of the reaction was further extended to the activated alkyl donor substituents, such as the 2-trialkylsilymethyl. In one representative example, the 2-*t*-butyldiphenylsilylmethyl cyclopropane **III-45l** was synthesized. It was hypothesized that the high level of diastereoselectivity could be achieved in the reactions due to the large size of the substituents on the silicon. When **III-45l** was subjected to previously optimized reaction condition, to our surprise, no product formation was observed. However, upon reacting under modified conditions, the product **III-46l** was formed in 82% yield, with only one observable diastereomer (Table 3.2, entry 5). This silyl group not only stabilizes the carbocation during the transition state through the β-silyl effect, but more importantly, acts as a point of further functionalization.

Next, the influence of a heteroatom-donating group on the cyclopropane was investigated. In particular, oxygen, sulfur and nitrogen groups were employed due to their established success in donor–acceptor cyclopropane chemistry.[21a,39] When a phthalimide group was the substituent, the desired cyclized product **III-46m** was obtained in 55% yield and 4.8:1 *dr* (Table 3.4, entry 1). This result is interesting since phthalimide group acts as a masked amine and thus provides handle for further functionalization. Heterocyclic aryl thioether structural motifs play important roles in biological and pharmaceutical areas.[40] Therefore, phenyl thioether **III-45n** was synthesized and subjected to modified cyclization condition to provide its cyclization product **III-46n** in 81% yield with 6.3:1 *dr* (Table 3.4, entry 2). The resulting thioether can be oxidized into a sulfoxide, which provides a point for further functionalization. Tetrahydrofuran, tetrahydropyran, and piperidinyl motifs are commonly found in an array of biologically active natural products. For this reason, we decided to examine cyclopropanes **III-45o**, **III-45p**, and **III-45q** derived from dihydrofuran, dihydropyran, and Cbz-protected 3,4-dihydropyridine, respectively. Cyclopropanes **III-45o** and **III-45p** readily cyclized to give products **III-46o**, **and III-46p** in 97 and 93% yield, respectively (Table 3.4, entry 3 and 4). In both cases, the major diastereomer had the all-*cis* configuration, as determined by NMR spectroscopy. Likewise, the Cbz-protected ring-fused piperidinyl cyclopropane **III-45q** afforded **III-46q** in 97% with a 7.1:1 *dr* (Table 3.4, entry 5). These experiments indicated that heteroatom-donating groups had a significant effect on the ability of cyclopropanes to undergo ring-opening, and provided the corresponding hydropyrido[1,2-*a*]indoles in high yields. This conclusion is in agreement with the observed reactivity of heteroatom-substituted cyclopropanes in the previous studies.

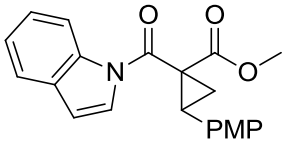
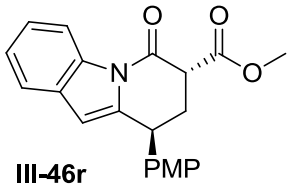
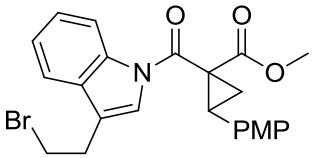
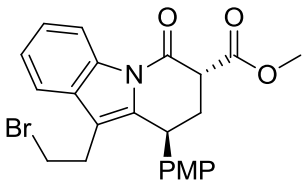
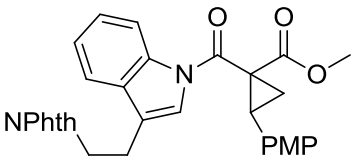
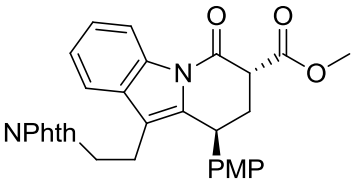
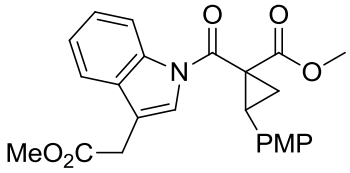
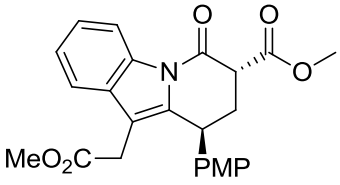
Table 3.4. Effect of Cyclopropyl Heteroatom-Substituents[a]

entry	substrate	product	time (h)	yield[b] (%)	*dr*[c] *(trans/cis)*
1[d]	 **III-45m**	 **III-46m**	8.0	55	4.8:1
2[d]	 **III-45n**	 **III-46n**	7.0	81	6.3:1
3	 **III-45o**	 **III-46o**	2.5	97	---[e,f]
4	 **III-45p**	 **III-46p**	2.5	93	---[e,f]
5	 **III-45q**	 **III-46q**	2.0	97	7.1:1[g]

[a] Reactions run with 1 equiv. substrate and 30 mol% $In(OTf)_3$ in DCM at 25 °C. [b] Isolated yields after column chromatography. [c] Diastereoselectivities determined from ^1H NMR of the crude reaction mixture and represent *trans:cis* diastereomeric ratios. [d] Reaction performed in 1,2-DCE at 80 °C. [e] Only one diastereomer visible by ^1H NMR. [f] All-cis diastereomer. [g] Major component is the all-*cis* diastereomer, minor component is its C(7) epimer.

To further demonstrate the modular nature of our protocol, the indole moiety was changed from 3-methyl indole (Table 3.5). To probe whether a substituent in the 3-position is not required for cyclization, cyclopropane **III-45r** (derived from indole) was tested in the reaction. Cyclization of substrate **III-45r** readily occurred to give **III-46r** in 99% yield with 1.1:1 *dr* (Table 3.5, entry 1).

Table 3.5. Effect of Indole Substituents on the Reaction Outcome[a]

entry	substrate	product	time (h)	yield[b] (%)	*dr*[c] *(trans/cis)*
1	 **III-45r**	 **III-46r**	0.75	99	1.1:1
2	 **III-45s**	 **III-46s**	1.0	99	2.7:1
3	 **III-45t**	 **III-46t**	2.0	76	2.8:1
4	 **III-45u**	 **III-46u**	3.0	88	2.0:1

[a] Reactions run with 1 equiv substrate and 30 mol% $In(OTf)_3$ in DCM at 25 °C. [b] Isolated yields after column chromatography. [c] Diastereoselectivities determined from ^1H NMR of the crude reaction mixture and represent *trans:cis* diastereomeric ratios.

Next, the 3-(2-bromoethyl)-1*H*-indole derived cyclopropane **III-45s** provided its cyclization product **III-46s** in near quantitative yield with 2.7:1 *dr* (Table 3.5, entry 2). The bromide remains intact throughout the cyclization and, thus, is available for further functionalization. Similarly, when the phthalimide-protected tryptamine derivative **III-45t** was subjected to the reaction conditions, hydropyrido[1,2-*a*]indole product **III-46t** was generated in 76% yield with 2.8:1 *dr* (Table 3.5, entry 3). This result is notable since the resulting product **III-46t** can be readily deprotected under standard conditions to provide the free amine. Lastly, the methyl acetate substituted indole derivative **III-45u** provided the cyclized product **III-46u** in 88% yield with 2.0:1 *dr* (Table 3.5, entry 4).

An interesting result was obtained when a geminally halo-alkyl disubstituted cyclopropane was examined. In one representative example, cyclopropane **III-45v** (from α-bromostyrene) was subjected to the reaction conditions, and pyrido[1,2-*a*]indole **III-47** was observed in 29% yield (Figure 3.13). This product seemingly arises from the rapid elimination of HBr from the cyclized intermediate **A** to generate the new aromatic ring. This result is notable as this method is also applicable to the direct synthesis of pyrido[1,2-*a*]indoles.

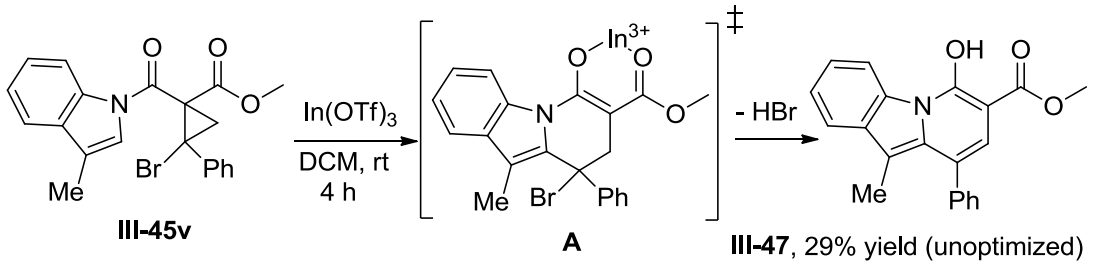


Figure 3.13. Synthesis of Pyrido[1,2-*a*]indoles Derivatives from Geminally Halo-Alkyl Disubstituted Cyclopropane

3.4. CONCLUSIONS

In conclusion, an efficient method for the facile generation of hydropyrido[1,2-*a*]indole based derivatives has been developed. An $In(OTf)_3$-catalyzes cyclopropane ring-opening/Friedel-Crafts alkylation sequence to provide these 1,2-annulated products in good to excellent yields (48-99%) in four steps from readily-available indoles and alkenes. The methodology is highly modular, operationally simple and amenable to a large variety of functional groups and substitution patterns. The new strategy for generation of hydropyrido[1,2-*a*]indole derivative should pave the way towards the synthesis of complex, biologically-active molecules.

3.5. EXPERIMENTAL

3.5.1. General Methods

All reactions were carried out in pre-dried glassware from the oven where additional moisture was removed by flame-drying the reaction vessel. Each reaction proceeded under a nitrogen atmosphere, and dry solvents were used, unless stated otherwise. Tetrahydrofuran and diethyl ether were distilled from a sodium/benzophenone ketyl under nitrogen and stored in a Schlenk flask. 1,2-Dichloroethane and dichloromethane were purified by distillation from calcium hydride under N_2 prior to use. Acetonitrile was dried by fractional distillation over CaH_2. Benzene was purified by drying with CaH_2. All other reagents were purchased from Acros, Sigma-Aldrich, Fluka, VWR, Merck, Alfa Aesar, TCI and Strem (for metal catalysts) and used without further purification.

Chromatographic purification was performed as flash chromatography with Silicycle silica gel (40-63 μm) and solvents indicated as eluent with 0.1-0.5 bar pressure. For quantitative flash chromatography, technical grade solvents were utilized. Analytical thin-layer chromatography (TLC) was performed on EMD silica gel 60 F_{254} TLC glass plates. Visualization was accomplished with UV light, aqueous basic potassium permanganate ($KMnO_4$) solution, iodine, aqueous acidic dinitrophenylhydrazine (DNP) solution, aqueous acidic *p*-anisaldehyde (PAA) solution, and ethanol solution of phosphomolybdic acid (PMA) followed by heating. Each yield refers to isolated analytically pure material.

Infrared (IR) spectra were obtained using a Nicolet 4700 FTIR with an ATR attachment from SmartOrbit Thermoelectronic Corp. The IR bands are characterized as

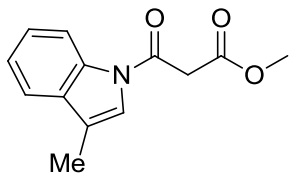
broad (br), weak (w), medium (m), and strong (s). Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Varian Mercury Vx 300 spectrometer or a Varian Mercury Vx 400 spectrometer with solvent resonances as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, t = triplet, m = multiplet), coupling constants (Hz), and integration. Mass spectra were obtained using a VG-70SE instrument. Diastereomeric ratios for cyclized products **III-46** were determined by ^{1}H NMR based on comparing the integral ratios of the benzylic protons (~4.0-5.0 ppm) for the two diastereomeric protons. The first signal represents the *trans* isomer and the second signal represents the *cis* isomer. This assignment is based on the coupling constants assigned from ^{1}H NMR in conjunction with decoupling experiments to assign all the coupled proton signals.

3.5.2. Experimental Procedures

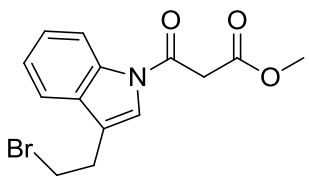
3.5.2.1. *N*-Acylation of Indole Compounds

Sodium hydride (1.1 equiv.) was suspended in THF (20 mL) and cooled to 0 $^\circ$C. In a separate flask, the desired indole (1.0 equiv.) was dissolved in 30 mL of THF and syringed into the reaction vessel. After 30 min, methyl-3-chloro-3-oxopropanoate (1.1 equiv.) was slowly added. The reaction was stirred for 14 h at room temperature. The reaction mixture was quenched with water. The organic layer was separated, and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried with anhydrous sodium sulfate, filtered, and concentrated under

reduced pressure. The residue was purified by silica gel flash chromatography for product isolation.

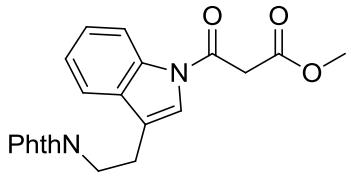


Methyl 3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (III-43a): The general procedure was followed using sodium hydride (1.90 g, 47.7 mmol), 3-methyl-1*H*-indole (5.00 g, 38.1 mmol), methyl-3-chloro-3-oxopropanoate (4.9 mL, 45.7 mmol), and THF (50 mL). After 14 h, the reaction was quenched, and column chromatography (20% EtOAc/Hex, R_f 0.26 and R_f 0.15 for keto and enol tautomers) afforded **III-43a** as a light brown solid (6.44 g, 73%). [**m.p.** 49-5 °C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.43 (d, *J* = 7.1 Hz, 1H), 7.52 – 7.47 (m, 1H), 7.41 – 7.28 (m, 2H), 7.10 (s, 1H), 3.92 (s, 2H), 3.79 (s, 3H), 2.27 (s, *J* = 1.3 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.8, 163.4, 136.0, 131.5, 125.5, 124.0, 121.4, 119.7, 118.9, 116.7, 52.9, 43.6, 9.7. **IR**: 3051.9 (w), 2937.6 (w), 1747.0 (s), 1685.1 (s), 1604.1 (w), 1447.0 (s), 1375.5 (s), 1232.6 (m), 1070.7 (m), 913.5 (m), 732.6 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 231.0895, Obs. 231.0895.



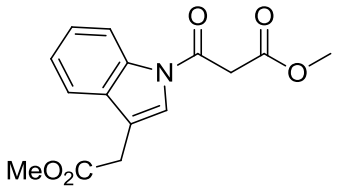
Methyl 3-(3-(2-bromoethyl)-1*H*-indol-1-yl)-3-oxopropanoate (III-43b):[41] A mixture of potassium carbonate (0.100 g, 0.724 mmol) and 3-(2-bromoethyl)-1*H*-indole (0.250 g,

1.1 mmol), methyl-3-chloro-3-oxopropanoate (0.21 mL, 1.95 mmol) and acetonitrile (13 mL) were heated to reflux. After 16 h, the reaction mixture was cooled, filtered and dried *in vacuo.* The residue was dissolved in EtOAc/Hex (1:2.5). The organic layer was separated, and the aqueous layer was extracted three times with EtOAc. The combined organic layers were dried with anhydrous sodium sulfate, filtered, and concentrated. Column chromatography (20% EtOAc/Hex, R_f 0.35) afforded **III-43b** as a yellow-brown solid (0.290 g, 81%). [**m.p.** 68-70 °C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.41 (d, *J* = 7.8 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.40 – 7.24 (m, 2H), 7.22 (s, 1H), 3.92 (s, 2H), 3.76 (s, 3H), 3.61 (t, *J* = 7.2 Hz, 2H), 3.22 (t, *J* = 7.2 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.5, 163.5, 135.7, 129.8, 125.6, 123.9, 122.1, 120.4, 118.4, 116.7, 52.7, 43.3, 31.1, 28.5. **IR**: 3091.7 (w), 2940.7 (w), 2878.8 (w), 1760.1 (s), 1657.8 (s), 1615.6 (s), 1535.5 (s), 1440.9 (s), 1239.4 (s), 1191.4 (s), 1040.8 (m), 820.8 (m), 777.4 (m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 323.0157, Obs. 323.0162.

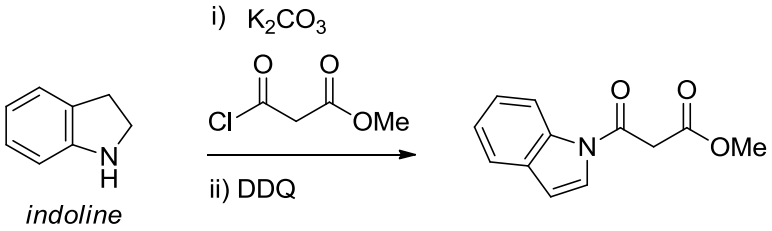


Methyl 3-(3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-1*H*-indol-1-yl)-3-oxopropanoate (III-43c): The general procedure was followed using sodium hydride (0.459 g, 11.5 mmol), 2-(2-(1*H*-indol-3-yl)ethyl)isoindoline-1,3-dione[42] (3.01 g, 10.4 mmol), methyl-3-chloro-3-oxopropanoate (1.4 mL, 13.0 mmol), and THF (90 mL). After 16 h, the reaction was quenched, and column chromatography (30% EtOAc/Hex, R_f 0.17) afforded **III-43c** as a white solid (1.69 g, 42%). [**m.p.** 138-140 °C] **^{1}H NMR**

(300 MHz, $CDCl_3$) δ 8.41 (d, *J* = 7.7 Hz, 1H), 7.88 – 7.77 (m, 2H), 7.75 – 7.67 (m, 2H), 7.64 (d, *J* = 7.7 Hz, 1H), 7.40 – 7.27 (m, 3H), 4.04 (t, *J* = 7.2 Hz, 2H), 3.96 (s, 2H), 3.78 (s, 3H), 3.10 (t, *J* = 7.4 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.0, 168.3, 167.2, 166.7, 163.7, 136.0, 134.1, 131.9, 130.4, 125.7, 124.2, 123.3, 121.9, 120.0, 118.9, 116.8, 52.9, 52.8, 43.4, 40.5, 37.2, 24.1. **IR**: 2937.6 (w), 1742.2 (s), 1703.2 (s), 1691.8 (s), 1599.3 (w), 1456.5 (m), 1383.6 (m), 1329.9 (m), 1210.0 (m), 1153.5 (s), 1008.8 (m), 923.1 (w), 719.7 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 390.1216, Obs. 390.1213.



Methyl 3-(3-(2-methoxy-2-oxoethyl)-1*H*-indol-1-yl)-3-oxopropanoate (III-43d): The general procedure was followed using sodium hydride (0.702 g, 17.6 mmol), methyl 2-(1*H*-indol-3-yl)acetate (3.00 g, 15.9 mmol), methyl-3-chloro-3-oxopropanoate (2.0 mL, 18.6 mmol), and THF (60 mL). After 16 h, the reaction was quenched, and column chromatography (30% EtOAc/Hex, R_f 0.24) afforded **III-43d** as a dark brown oil (3.55 g, 77%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.43 (d, *J* = 8.0 Hz, 1H), 7.57 – 7.49 (m, 1H), 7.43 – 7.27 (m, 3H), 3.96 (s, 2H), 3.79 (s, 3H), 3.73 (s, 2H), 3.72 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.0, 166.6, 163.6, 135.8, 130.1, 125.8, 124.2, 123.1, 118.9, 116.8, 116.0, 52.8, 52.2, 43.4, 30.6. **IR**: 3009.3 (w), 2952.1 (w), 1737.4 (s), 1703.2 (s), 1595.1 (m), 1366.0 (s), 1265.7 (m), 1204.7 (s), 1148.4 (s), 1015.7 (m), 909.4 (m), 728.3 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 289.0950, Obs. 289.0945.



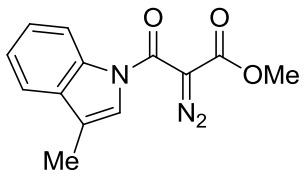
Methyl 3-(1*H*-indol-1-yl)-3-oxopropanoate (III-43e): Following a modification of Kerr's reported procedure,[24a] indoline (4.0 g, 33.56 mmol) was dissolved in THF (70 mL) in a round bottom flask equipped with a magnetic stir bar. K_2CO_3 (9.28 g, 67.14 mmol) was added and the mixture was cooled to 0^oC. Methyl malonyl chloride (3.977mL, 37.09 mmol) was added drop-wise with rapid stirring. Formation of white precipitate was immediately observed. After 30 min, the reaction mixture was filtered, and the solvent was removed under reduced pressure to yield the indoline β-amide ester, which was used without purification.

In a dry round bottom flask equipped with a reflux condenser, the resulting β-amide ester (4.26 g, 19.43 mmol) was dissolved in dry toluene (55 mL), and DDQ (5.28 g, 23.26 mmol) was added. The reaction mixture was heated to a reflux for 12 hours. The reaction was cooled to room temperature, diluted with EtOAc, washed with water and brine and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* and purification of the crude reaction mixture by flash column chromatography (15% EtOAc/Hex, R_f 0.35) yielded **III-43e** as a yellow-brown oil (2.72 g, 37.3% over the two steps). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.44 (d, *J* = 8.1 Hz, 1H), 7.56 – 7.51 (m, 1H), 7.38 – 7.23 (m, 3H), 6.61 (dd, *J* = 3.8, 0.8 Hz, 1H), 3.91 (s, 2H), 3.74 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.5, 163.8, 135.4, 130.2, 125.1, 124.5, 123.9, 120.7, 116.3, 109.8, 52.6, 43.1. **IR**: 3109.7 (w), 3152.9 (w), 3036.6 (w), 2953.6 (w), 2850.7 (w), 1737.9 (m),

1703.1 (s), 1691.8 (m), 1529.04 (w), 1472.2 (w), 1450.6 (m), 1383.1 (m), 1346.9 (s), 1261.2 (m), 1204.9 (s), 1150.2 (s), 1015.7 (m), 925.7 (m), 747.3 (s), 715.2 (m), 689.3 (m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 217.0739, Obs. 217.0738.

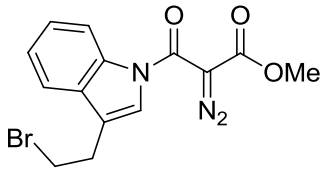
3.5.2.2. Formation of the Diazo Compounds

The β-amide ester (1.0 equiv.) was dissolved in acetonitrile. Triethylamine (1.2 equiv.) was added to the reaction mixture and stirred for 10 min. Tosyl azide (1.2 equiv.) was placed in the reaction flask. The mixture was stirred at room temperature for 12 h and concentrated under reduced pressure. The resulting residue was purified by silica gel flash chromatography to afford the diazo compound **III-44**.

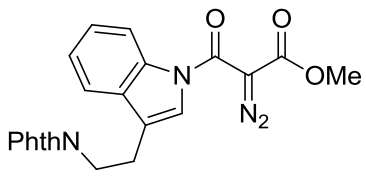


Methyl 2-diazo-3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (III-44a): The general procedure was followed using methyl 3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (2.71 g, 11.7 mmol), triethylamine (2.0 mL, 14.4 mmol), tosyl azide (2.81 g. 14.2 mmol), and acetonitrile (30 mL). After 12 h, the reaction mixture was concentrated, and column chromatography (20% EtOAc/Hex, R_f 0.41) afforded **III-44a** as a yellow solid (2.79 g, 93%). [**m.p.** 74-76 °C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.6 Hz, 1H), 7.51 – 7.47 (m, 1H), 7.39 – 7.26 (m, 2H), 7.11 (s, 1H), 3.85 (s, 3H), 2.28 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 161.5, 158.9, 136.0, 131.7, 124.8, 123.7, 123.3, 118.9, 117.7, 115.7, 69.7, 52.6, 9.7. **IR**: 3047.1 (w), 2956.6 (w), 2918.5 (w), 2132.7 (s), 1708.9 (s), 1651.7 (s),

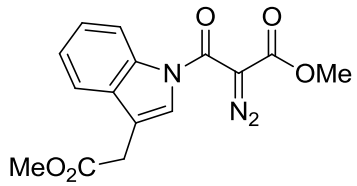
1601.0 (m), 1466.0 (s), 1349.6 (s), 1302.9 (s), 1254.3(s), 1127.9(s), 1046.9 (s), 865.9 (m), 732.7 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 257.0800, Obs. 257.0805.



Methyl 3-(3-(2-bromoethyl)-1*H*-indol-1-yl)-2-diazo-3-oxopropanoate (III-43b): The general procedure was followed using methyl 3-(3-(2-bromoethyl)-1*H*-indol-1-yl)-3-oxopropanoate (0.110 g, 0.339 mmol), triethylamine (0.0412 g, 0.407 mmol), tosyl azide (0.080 g, 0.407 mmol), and acetonitrile (10 mL). After 16 h, the reaction mixture was concentrated, and column chromatography (20% EtOAc/Hex, R_f 0.50) afforded **III-43b** as a yellow oil (0.104 g, 88%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.36 – 7.23 (m, 2H), 7.22 (s, 1H), 3.81 (s, 3H), 3.61 (t, *J* = 7.3 Hz, 2H), 3.23 (t, *J* = 7.2 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 161.2, 159.1, 136.0, 130.1, 125.0, 124.2, 123.8, 118.7, 118.5, 115.8, 70.1, 52.7, 31.2, 28.7. **IR**: 3018.6 (w), 2947.1, (w), 2142.0 (s), 1732.7 (s), 1656.5 (s), 1604.1 (w), 1451.7 (s), 1380.4 (s), 1306.8 (s), 1251.7 (m), 1056.4 (m), 861.2 (w), 734.3 (s), 708.8 (m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 349.0062, Obs. 349.0061.

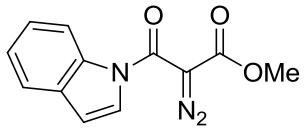


Methyl 2-diazo-3-(3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-1*H*-indol-1-yl)-3-oxo propanoate (III-43c): The general procedure was followed using methyl 3-(3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-1*H*-indol-1-yl)-3-oxopropanoate (1.48 g, 3.78 mmol), triethylamine (700 μL, 5.02 mmol), tosyl azide (0.896 g, 4.54 mmol), and acetonitrile (20 mL). After 18 h, the reaction mixture was concentrated, and column chromatography (40% EtOAc/Hex, R_f 0.44) afforded **III-43c** as a yellow-brown solid (1.49 g, 95%). [**m.p.** 98-100 °C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.18 – 8.13 (m, 1H), 7.86 – 7.80 (m, 2H), 7.74 – 7.64 (m, 3H), 7.37 – 7.27 (m, 2H), 7.23 (s, 1H), 4.00 (t, J = 6.0 Hz, 2H), 3.81 (s, 3H), 3.10 (t, J = 6.0 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) (Rotamers!!!) δ 168.2, 161.2, 159.2, 136.1, 133.9, 133.8, 132.1, 130.5, 125.0, 124.1, 123.9, 123.2, 123.1, 122.1, 122.0, 119.4, 119.0, 118.8, 118.0, 115.8, 112.4, 111.1, 69.8, 52.7, 38.5, 37.4, 24.4, 24.2. **IR**: 3032.8 (s), 2942.4 (w), 2137.5 (s), 1708.4 (s), 1642.2 (m), 1604.1 (w), 1451.7 (w), 1379.6 (s), 1306.8 (s), 1256.4 (m), 1170.7 (m), 1095.3 (m), 1004.0 (w), 861.2 (m), 732.4 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 416.1121, Obs. 416.1105.



Methyl 2-diazo-3-(3-(2-methoxy-2-oxoethyl)-1*H*-indol-1-yl)-3-oxopropanoate (III-43d): The general procedure was followed using methyl 3-(3-(2-methoxy-2-oxoethyl)-1*H*-indol-1-yl)-3-oxopropanoate (1.49 g, 5.16 mmol), triethylamine (880 μL, 6.31 mmol), tosyl azide (1.22 g, 6.19 mmol), and acetonitrile (20 mL). After 18 h, the reaction mixture was concentrated, and column chromatography (40% EtOAc/Hex, R_f 0.43)

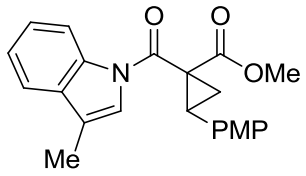
afforded **III-43d** as a brown solid (1.36 g, 83%). [**m.p.** 77-79 °C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.17 (d, *J* = 7.8 Hz, 1H), 7.52 (d, *J* = 7.7 Hz, 1H), 7.41 – 7.26 (m, 3H), 3.84 (s, 3H), 3.73 (s, 2H), 3.72 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.1, 161.3, 159.2, 135.9, 130.3, 125.2, 125.1, 123.9, 118.9, 115.8, 114.1, 70.1, 52.7, 52.1, 30.7. **IR**: 2999.5 (w), 2961.4 (w), 2137.5 (s), 1721.8 (s), 1637.44 (s), 1599.3 (w), 1446.9 (s), 1364.2 (s), 1305.1 (s), 1253.8 (s), 1139.6 (s), 1051.6 (w), 870.7 (m), 747.9 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 315.0855, Obs. 315.0860.



Methyl 2-diazo-3-(1*H*-indol-1-yl)-3-oxopropanoate (III-43e): The general procedure was followed using methyl 3-(1*H*-indol-1-yl)-3-oxopropanoate (1.42 g, 6.54 mmol), triethylamine (1.82 mL, 13.07 mmol), tosyl azide (1.547 g, 7.845 mmol), and acetonitrile (30 mL). After 12 h, the reaction mixture was concentrated, and column chromatography (10% EtOAc/Hex, R_f 0.35) afforded **III-43e** as a yellow oil (1.49 g, 93.7%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.22 – 8.16 (m, 1H), 7.59 – 7.53 (m, 1H), 7.40 – 7.23 (m, 3H), 6.61 (dd, *J* = 3.8, 0.7 Hz, 1H), 3.83 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 161.3, 159.5, 135.7, 130.6, 127.4, 126.7, 124.7, 123.8, 120.9, 115.5, 108.2, 52.7. **IR**: 3162.8 (w), 3053.2 (w), 2953.6 (w), 2140.3 (s), 1710.8 (s), 1721.3 (s), 1657.8 (s), 1649.7 (s), 1529.0 (w), 1451.1 (s), 1380.5 (s), 1342.4 (s), 1298.4 (s), 1244.9 (m), 1139.5 (m), 1121.6 (m), 1090.6 (m), 1067.0 (m), 945.5 (w), 883.1 (m), 859.7 (m), 746.5 (s), 640.3 (w) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 243.0644, Obs. 243.0640.

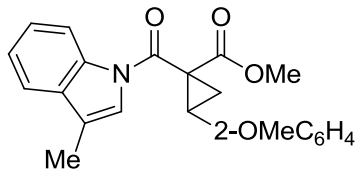
3.5.2.3. Synthesis of the Cyclopropanes

The cyclopropanes were prepared using a modified version of Gonzalez-Bobes' protocol:[34] A round bottom flask was charged with Rh_2esp_2 (0.1 mol%) and a magnetic stir bar. DCM (2.0 mL) was added to the flask. The reaction vessel was cooled to 0°C, and the corresponding alkene (1.0 equiv.) was added. After 10 min, the diazo reagent (1.3 equiv.) was dissolved in DCM (5 mL) and syringed into the reaction mixture. After 10 min, the ice bath was removed and the reaction proceeded at room temperature. Upon completion (monitored by TLC) or 12 h of reactivity, the reaction was quenched with saturated thiourea and stirred for 30 min. The organic layer was separated, and the aqueous layer extracted three times with DCM. The combined organic layers were washed with brine, dried with anhydrous sodium sulfate, filtered, concentrated under reduced pressure. The residue was purified by silica gel flash chromatography.

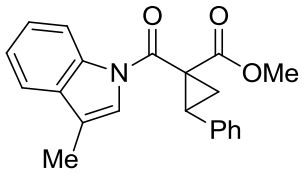


Methyl 2-(4-methoxyphenyl)-1-(3-methyl-1*H*-indole-1-carbonyl) cyclopropane carboxylate (III-45a): The general procedure was followed using 4-methoxystyrene (0.201 g, 1.49 mmol), methyl 2-diazo-3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.500 g, 1.94 mmol), Rh_2esp_2 (1.5 mg, 1.98 μmol) and DCM (8 mL). After 12 h, the reaction was quenched, and column chromatography (20% EtOAc/Hex, R_f 0.52) afforded **III-45a** as a pale yellow solid (0.328 g, 60%). [**m.p.** 110-112 °C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.45 (d, *J* = 8.0 Hz, 1H), 7.61 - 7.45 (m, 1H), 7.44 – 7.26 (m, 5H), 6.90 – 6.83 (m, 2H), 3.81 (s, 3H), 3.41 (t, *J* = 4Hz, 1H), 3.41 (s, 3H), 2.40 (dd, *J* = 8.3, 5.2 Hz, 1H),

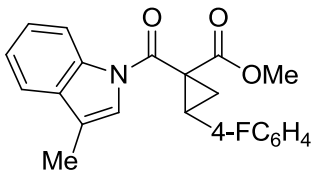
2.28 (s, 3H), 1.82 (dd, *J* = 9.3, 5.2 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.0, 165.8, 158.9, 136.0, 131.5, 130.2, 126.1, 125.4, 123.8, 121.5, 119.2, 118.9, 116.5, 113.6, 55.2, 52.8, 39.5, 31.1, 18.8, 9.8. **IR**: 3050.0 (w), 2914.3 (m), 1742.9 (m), 1681.0 (s), 1600.0 (m), 1514.29 (m), 1450.0 (s), 1346.3 (s), 1246.8 (s), 1176.5 (s), 1028.6 (s), 838.1 (s), 748.2 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 363.1471, Obs. 363.1471.



Methyl 2-(2-methoxyphenyl)-1-(3-methyl-1*H*-indole-1-carbonyl)cyclopropane carboxylate (III-45b): The general procdure was followed using 1-methoxy-2-vinylbenzene (0.095 g, 0.709 mmol), methyl 2-diazo-3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.210 g, 0.816 mmol), Rh_2esp_2 (1.0 mg, 1.31 μmol), and DCM (10 mL). After 12 h, the reaction was quenched, and column chromatography (20% EtOAc/Hex, R_f 0.35) afforded **III-45b** as a pale yellow solid (0.196 g, 76%). [**m.p.** 106-108 °C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.54 (d, *J* = 7.9 Hz, 1H), 7.57 – 7.27 (m, 6H), 7.04 – 6.95 (m, 1H), 6.91 (d, *J* = 8.2 Hz, 1H), 3.88 (s, 3H), 3.45 (s, 3H), 3.45 (t, 1H), 2.35 (dd, *J* = 7.9, 4.5 Hz, 1H), 2.32 (d, *J* = 1.3 Hz, 3H), 1.97 (dd, *J* = 9.3, 5.0 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.4, 165.9, 158.5, 136.0, 131.4, 130.0, 129.7, 128.7, 127.7, 125.0, 123.5, 122.8, 122.2, 120.0, 118.6, 118.1, 116.5, 109.9, 66.7, 55.2, 52.4, 38.0, 28.3, 21.5, 19.0, 14.6, 9.7. **IR**: 3059.9 (w), 2983.6 (w), 1720.3 (s), 1658.0 (s), 1441.1 (s), 1338.7 (s), 1233.7 (m), 712.5 (s), 674.4 (m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 363.1471, Obs. 363.1471.

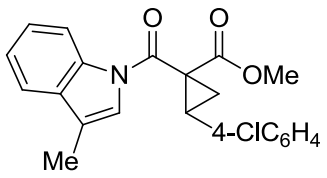


Methyl 1-(3-methyl-1*H*-indole-1-carbonyl)-2-phenylcyclopropanecarboxylate (III-45c): The general procedure was followed using styrene (0.100 g, 0.960 mmol), methyl 2-diazo-3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.329 g, 1.28 mmol), Rh_2esp_2 (1.0 mg, 1.32 μmol), and DCM (13 mL). After 12 h, the reaction was quenched, and column chromatography (20% EtOAc/Hex, R_f 0.60) afforded **III-45c** as a white solid (0.273 g, 85%). [**m.p.** 130-132 °C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.46 (d, *J* = 8.0 Hz, 1H), 7.55 – 7.48 (m, 1H), 7.45 – 7.26 (m, 8H), 3.48 (t, *J* = 8.8 Hz, 1H), 3.40 (s, 3H), 2.46 (dd, *J* = 8.3, 5.2 Hz, 1H), 2.29 (s, 3H), 1.84 (dd, *J* = 9.3, 5.2 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.9, 165.6, 136.0, 134.2, 131.5, 129.1, 128.2, 127.4, 125.4, 123.8, 121.4, 119.2, 118.9, 116.5, 52.8, 39.5, 31.5, 18.5, 9.8. **IR**: 3037.6 (w), 2951.9 (w), 2918.5 (w), 1732.7 (s), 1692.0 (s), 1446.9 (s), 1390.8 (s), 1348.3 (s), 1208.8 (m), 1051.6 (m), 742.1 (m), 684.9 (m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 333.1365, Obs. 333.1367.



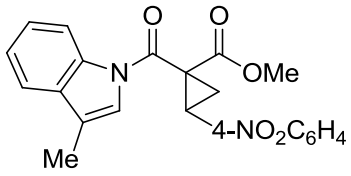
Methyl 2-(4-fluorophenyl)-1-(3-methyl-1*H*-indole-1-carbonyl)cyclopropane carboxylate (III-45d): The general procedure was followed using 4-fluorostyrene (0.146 g, 1.19 mmol), methyl 2-diazo-3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.356 g, 1.38 mmol), Rh_2esp_2 (1.6 mg, 2.10 μmol), and DCM (8 mL). After 10 h, the reaction was

quenched, and column chromatography (20% EtOAc/Hex, R_f 0.64) afforded **III-45d** as a pale green solid (0.273 g, 65%). [**m.p.** 120-122 °C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.45 (d, *J* = 8.0 Hz, 1H), 7.52 (d, *J* = 8.3 Hz, 1H), 7.44 – 7.29 (m, 4H), 7.25 (s, 1H), 7.07 – 6.98 (m, 2H), 3.46 (t, *J* = 8.5 Hz, 1H), 3.42 (s, 3H), 2.42 (dd, *J* = 8.2, 5.3 Hz, 1H), 2.29 (s, 3H), 1.84 (dd, *J* = 9.3, 5.3 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.8, 165.4, 163.8, 160.5, 136.0, 131.5, 130.7, 130.0, 125.4, 123.9, 121.3, 119.4, 118.9, 116.5, 115.3, 115.0, 52.9, 39.5, 30.8, 18.7, 9.8. **IR**: 3010.0 (w), 2947.1 (w), 2904.3 (w), 1727.9 (m), 1685.1 (s), 1518.4 (s), 1456.5 (s), 1399.3 (s), 1337.4 (s), 1215.2 (s), 1146.9 (s), 1051.7 (m), 846.9 (m), 723.1 (s), 608.7 (m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 351.1271, Obs. 351.1268.

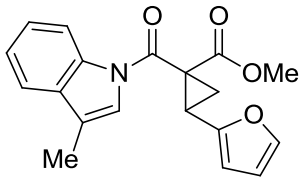


Methyl 2-(4-chlorophenyl)-1-(3-methyl-1*H*-indole-1-carbonyl)cyclopropane carboxylate (III-45e): The general procedure was followed using 4-chlorostyrene (0.124 g, 0.898 mmol), methyl 2-diazo-3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.250 g, 0.973 mmol), Rh_2esp_2 (1.5 mg, 1.71 μmol), and DCM (8 mL). After 12 h, the reaction was quenched, and column chromatography (20% EtOAc/Hex, R_f 0.64) afforded **III-45e** as a white solid (0.275 g, 83%). [**m.p.** 129-131 °C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.46 (d, *J* = 8.0 Hz, 1H), 7.55 – 7.50 (m, 1H), 7.45 – 7.29 (m, 6H), 7.26 (d, *J* = 1.3 Hz, 1H), 3.44 (t, J = 6.8 Hz, 1H), 3.44 (s, 3H), 2.43 (dd, *J* = 8.3, 5.3 Hz, 1H), 2.30 (s, 3H), 1.86 (dd, *J* = 9.3, 5.3 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.7, 165.3, 136.0, 133.3,

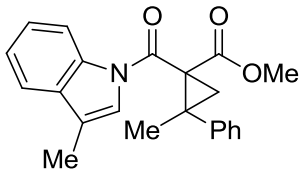
132.8, 131.5, 130.4, 128.3, 125.4, 123.9, 121.2, 119.4, 118.9, 116.5, 52.9, 39.5, 30.8, 18.6, 9.7. **IR**: 3010.0 (w), 2951.9 (w), 2913.8 (w), 1727.9 (s), 1691.9 (s), 1485.0 (m), 1451.0 (s), 1389.9 (s), 1347.9 (s), 1218.3 (m), 1156.4 (m), 1080.2 (m), 842.1 (m), 742.1 (m) 708.7 (w) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 367.0975, Obs. 367.0981.



Methyl 1-(3-methyl-1*H*-indole-1-carbonyl)-2-(4-nitrophenyl)cyclopropane carboxylate (III-45f): The general procedure was followed using 4-nitrostyrene (0.252 g, 1.69 mmol), methyl 2-diazo-3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.505 g, 1.97 mmol), Rh_2esp_2 (1.2 mg, 1.98 μmol), and DCM (8 mL). After 10 h, the reaction was quenched, and column chromatography (20% EtOAc/Hex, R_f 0.69) afforded **III-45f** as a yellow solid (0.325 g, 51%). [**m.p.** 163-165 °C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.43 (d, *J* = 7.9 Hz, 1H), 8.24 – 8.17 (m, 2H), 7.58 – 7.50 (m, 3H), 7.45 – 7.30 (m, 2H), 7.21 (s, 1H), 3.54 (t, *J* = 8.8 Hz, 1H), 3.43 (s, 3H), 2.51 (dd, *J* = 8.3, 5.4 Hz, 1H), 2.29 (s, 3H), 1.94 (dd, *J* = 9.2, 5.4 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.5, 164.8, 147.3, 142.0, 136.0, 131.5, 130.0, 125.6, 124.1, 123.4, 120.9, 119.8, 119.0, 116.5, 53.1, 40.0, 30.9, 18.9, 9.8. **IR:** 3000.0 (w), 2913.8 (w), 2851.9 (w), 1727.9 (m), 1691.2 (s), 1599.3 (m), 1508.9 (s), 1449.8 (s), 1390.3 (s), 1342.9 (s), 1216.9 (s), 1142.1 (m), 1046.9 (m), 856.4 (m), 736.7 (s), 699.2 (m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 378.1216, Obs. 378.1208.

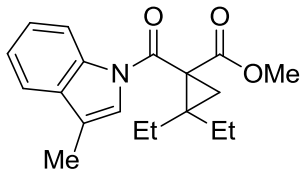


Methyl 2-(furan-2-yl)-1-(3-methyl-1*H*-indole-1-carbonyl)cyclopropanecarboxylate (III-45g): The general procedure was followed using 2-vinylfuran (0.059 g, 0.627 mmol), methyl 2-diazo-3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.210 g, 0.816 mmol), Rh_2esp_2 (1.0 mg, 1.31 μmol), and DCM (10 mL). After 12 h, the reaction was quenched, and column chromatography (15% EtOAc/Hex, R_f 0.35) afforded **III-45g** as a white solid (0.084 g, 41%). [**m.p.** 95-97 °C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.45 (d, *J* = 7.9 Hz, 1H), 7.56 – 7.50 (m, 1H), 7.44 – 7.30 (m, 4H), 6.41 – 6.35 (m, 1H), 6.32 – 6.28 (m, 1H), 3.54 (s, 3H), 3.25 (t, *J* = 8.7 Hz, 1H), 2.34 (dd, *J* = 6.9, 4.2 Hz, 1H), 2.31 (d, *J* = 1.3 Hz, 3H), 1.96 (dd, *J* = 9.5, 5.2 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) 167.6, 164.9, 149.1, 142.3, 136.0, 131.5, 125.3, 123.9, 121.7, 119.3, 118.8, 116.5, 110.5, 108.8, 52.9, 38.2, 24.7, 18.7, 9.8. **IR**: 3086.97 (w), 2972.5 (w), 1726.4 (m), 1711.4 (m), 1441.3 (m), 1382.7 (m), 759.9 (s), 663.0 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 323.1158, Obs. 323.1159.



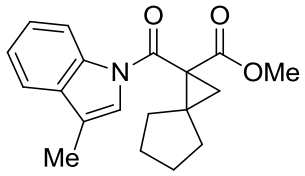
Methyl 2-methyl-1-(3-methyl-1*H*-indole-1-carbonyl)-2-phenylcyclopropane carboxylate (III-45h): The general procedure was followed using prop-1-en-2-ylbenzene (0.123 g, 1.046 mmol), methyl 2-diazo-3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate

(0.350 g, 1.360 mmol), Rh_2esp_2 (1.0 mg, 1.31 μmol), and DCM (10 mL). After 12 h, the reaction was quenched, and column chromatography (20% EtOAc/Hex, R_f 0.38) afforded **III-45h** as a colorless oil (0.225 g, 62%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.61 (d, *J* = 7.8 Hz, 0.90), 7.88 – 7.80 (m, 0.16), 7.63 – 7.55 (m, 1.05), 7.54 – 7.28 (m, 8.37), 7.24 – 7.20 (m, 0.51), 3.69 (s, 0.40), 3.46 (d, *J* = 0.8 Hz, 3), 2.67 (d, *J* = 5.5 Hz, 0.14), 2.53 (d, *J* = 5.1 Hz, 1.33), 2.39 (s, 2.99), 2.26 (d, *J* = 1.3 Hz, 0.42), 1.96 (d, *J* = 6.6 Hz, 0.55) 1.85 (d, *J* = 5.1 Hz, 1.03), 1.64 (s, 0.27), 1.55 (s, 2.91). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.4, 164.9, 140.6, 136.0, 131.5, 128.4, 128.0, 127.8, 127.2, 125.3, 123.8, 122.3, 118.8, 118.7, 116.8, 52.6, 41.9, 38.4, 26.0, 25.7, 9.8. **IR**: 3080.6 (w), 2939.6 (w), 2896.9 (w), 1724.3 (s), 1657.6 (s), 1421.8 (s), 1382.7 (s), 1267.7 (s), 789.5 (s), 664.3 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 347.1521, Obs. 347.1516.

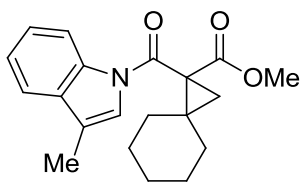


Methyl 2,2-diethyl-1-(3-methyl-1*H*-indole-1-carbonyl)cyclopropanecarboxylate (III-45i): The general procedure was followed using 3-methylenepentane (0.062 g, 0.747 mmol), methyl 2-diazo-3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.250 g, 0.971 mmol), Rh_2esp_2 (1.0 mg, 1.31 μmol), and DCM (10 mL). After 12 h, the reaction was quenched, and column chromatography (15% EtOAc/Hex, R_f 0.35) afforded **III-45i** as a white solid (0.117 g, 50%). [**m.p.** 78–80 ^{o}C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.40 (d, *J* = 8.0 Hz, 1H), 7.45 – 7.39 (m, 1H), 7.33 – 7.21 (m, 3H), 3.58 (s, 3H), 2.21 (d, *J* = 1.3 Hz, 3H), 1.97 – 1.73 (m, 3H), 1.62 (dd, *J* = 4.8, 1.2 Hz, 1H), 1.51 (d, *J* = 4.8 Hz, 1H), 0.99 (t,

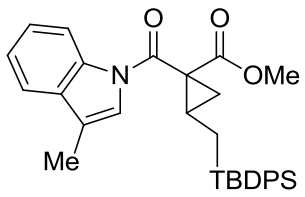
J = 7.5 Hz, 3H), 0.91 – 0.71 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.7, 165.7, 135.9, 131.4, 125.0, 123.6, 122.7, 118.6, 118.0, 116.7, 52.6, 41.4, 40.1, 27.4, 26.2, 21.5, 10.7, 10.6, 9.7. **IR**: 3059.7 (w), 2946.2 (m), 1714.5 (s), 1657.6 (s), 1414.8 (s), 1381.3 (s), 1292.4 (s), 1081.2 (s), 728.5 (s), 663.3 (m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 313.1678, Obs. 313.1683.



Methyl 1-(3-methyl-1*H*-indole-1-carbonyl)spiro[2.4]heptane-1-carboxylate (III-45j): The general procedure was followed using methylenecyclopentane (0.098 g, 1.20 mmol), methyl 2-diazo-3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.400 g, 1.55 mmol), Rh_2esp_2 (1.0 mg, 1.31 μmol), and DCM (10 mL). After 4 h, the reaction was quenched, and column chromatography (15% EtOAc/Hex, R_f 0.35) afforded **III-45j** as a colorless oil (0.342 g, 92%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.55 – 7.48 (m, 1H), 7.43 – 7.27 (m, 2H), 7.10 (s, 1H), 3.65 (s, 3H), 2.31 (s, 3H), 2.24 – 1.98 (m, 2H), 1.90 – 1.62 (m, 7H), 1.46 – 1.33 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.1, 165.6, 135.7, 131.2, 124.9, 123.4, 121.9, 118.5, 118.3, 116.3, 52.2, 40.0, 39.2, 34.4, 34.2, 33.6, 31.6, 31.3, 29.0, 25.5, 25.5, 25.0, 22.4, 20.4, 13.9, 9.5. **IR**: 3040.0 (w), 2892.6 (w), 1765.3 (s), 1711.65 (s), 1439.1 (s), 1359.7 (s), 715.5 (s), 662.9 (m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 311.1521, Obs. 311.1515.

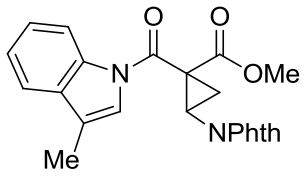


Methyl 1-(3-methyl-1*H*-indole-1-carbonyl)spiro[2.5]octane-1-carboxylate (III-45k): The general procedure was followed using methylenecyclohexane (0.068 g, 0. 709 mmol), methyl 2-diazo-3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.210 g, 0.816 mmol), Rh_2esp_2 (1.0 mg, 1.31 μmol), and DCM (10 mL). After 6 h, the reaction was quenched, and column chromatography (15% EtOAc/Hex, R_f 0.40) afforded **III-45k** as a white solid (0.160 g, 69%). [**m.p**. 120-122 ^oC]. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.49 (d, *J* = 5.7 Hz, 1H), 7.60 – 7.48 (m, 1H), 7.44 – 7.27 (m, 2H), 7.14 (s, 1H), 3.65 (s, 3H), 2.32 (d, *J* = 1.2 Hz, 3H), 2.18 (d, *J* = 12.5 Hz, 1H), 1.92 – 1.21 (m, 10H), 1.05 – 0.94 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.5, 165.7, 135.8, 131.4, 125.0, 123.5, 122.5, 118.6, 118.2, 116.5, 52.5, 41.1, 37.5, 33.9, 28.7, 26.4, 25.8, 25.6, 25.5, 9.7. **IR**: 2998.1 (w), 2878.5 (w), 1720.8 (m), 1711.4 (m), 1439.8 (m), 1340.7 (m), 1138.1 (w), 759.5 (s), 674.3 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 325.1678, Obs. 325.1681.



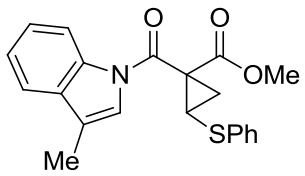
Methyl 2-((*tert*-butyldiphenylsilyl)methyl)-1-(3-methyl-1*H*-indole-1-carbonyl) cyclopropanecarboxylate (III-45l): The general procedure was followed using allyl(*tert*-butyl)diphenylsilane (0.294 g, 1.05 mmol), methyl 2-diazo-3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.350 g, 1.36 mmol), Rh_2esp_2 (1.0 mg, 1.31 μmol), and DCM (8 mL). After 6 h, the reaction was quenched, and column chromatography (20% EtOAc/Hex, R_f 0.45) afforded **III-45l** as a white solid (0.332 g, 62%). [**m.p.** 127-129 ^oC] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.39 (d, *J* = 7.9 Hz, 1H), 7.76 – 7.64 (m, 4H), 7.57 – 7.23

(m, 9H), 7.17 (s, 1H), 3.69 (s, 3H), 2.28 (s, 3H), 1.74 – 1.66 (m, 1H), 1.57 – 1.40 (m, 2H), 1.31 (dd, *J* = 8.5, 5.5 Hz, 2H), 1.13 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.6, 166.3, 136.0, 136.9, 135.8, 134.1, 133.8, 131.4, 129.3, 129.2, 127.7, 127.6, 125.1, 123.6, 121.6, 118.7, 118.6, 116.4, 52.7, 37.3, 27.8, 25.7, 23.0, 18.1, 9.7, 8.0. **IR**: 3066.2 (w), 2932.8 (m), 2842.4 (m), 1728.1 (s), 1692.7 (s), 1451.6 (s), 1389.5 (m), 1348.5 (s), 1213.1 (m), 1153.3 (m), 1106.0 (m), 818.3 (w), 749.1 (m), 701.5 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 509.2386, Obs. 509.2388.

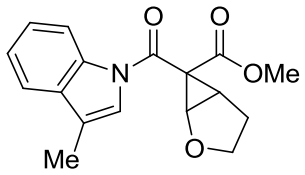


Methyl 2-(1,3-dioxoisoindolin-2-yl)-1-(3-methyl-1*H*-indole-1-carbonyl)cyclopropane carboxylate (III-45m): The general procedure was followed using N-vinyl-phthalimide (0.155 g, 897 μmol), methyl 2-diazo-3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.300 g, 1.17 mmol), Rh_2esp_2 (1.1 mg, 1.45 μmol), and DCM (8 mL). After 12 h, the reaction was quenched, and column chromatography (20% EtOAc/Hex, R_f 0.20) afforded **III-45m** as a white solid (0.247 g, 68%). [**m.p.** 88-90 ^oC] *Diastereomeric Ratio*: (2.5:1). **^{1}H NMR** (300 MHz, $CDCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (d, *J* = 7.4 Hz, 0.83), 8.22 (d, *J* = 6.1 Hz, 0.27), 7.98 (s, 1.00), 7.83 (dt, *J* = 6.9, 3.5 Hz, 2.19), 7.76 – 7.66 (m, 2.80), 7.66 – 7.58 (m, 1.00), 7.51 – 7.45 (m, 1.16), 7.42 – 7.18 (m, 3.88), 4.16 (dd, *J* = 9.2, 6.8 Hz, 0.23), 3.71 (s, 1.11), 3.67 (dd, *J* = 8.0, 6.5 Hz, 1.18), 3.57 (s, 3.00), 3.47 (t, *J* = 6.5 Hz, 0.63), 2.59 (t, *J* = 6.4 Hz, 1.00), 2.35 – 2.27 (m, 4.00), 2.23 (s, 1.45), 2.17 (dd, *J* = 9.2, 6.2 Hz, 0.60). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.7, 168.2, 168.0, 167.8, 164.0, 136.0, 134.3, 134.2, 134.2, 131.8, 131.4, 131.3, 125.3, 125.1, 124.0, 123.8, 123.6, 123.4, 122.5,

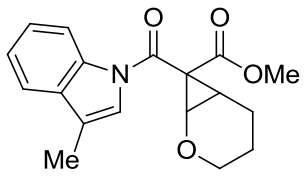
122.1, 119.0, 118.9, 118.8, 118.7, 116.5, 116.3, 53.4, 53.3, 48.8, 35.9, 33.9, 20.6, 17.4, 9.8, 9.6. **IR**: 3056.7 (w), 2951.9 (w), 1770.8 (w), 1720.5 (s), 1680.3 (s), 1604.1 (w), 1442.2 (m), 1389.3 (s), 1308.8 (s), 1223.1 (s), 1070.7 (m), 970.7 (w), 865.9 (w), 714.8 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 402.1216, Obs. 402.1213.



Methyl 1-(3-methyl-1*H*-indole-1-carbonyl)-2-(phenylthio)cyclopropanecarboxylate (III-45n): The general procedure was followed using phenyl(vinyl)sulfane (0.311 g, 2.29 mmol), methyl 2-diazo-3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.722 g, 2.81 mmol), Rh_2esp_2 (1.8 mg, 2.4 μmol), and DCM (13 mL). After 12 h, the reaction was quenched, and column chromatography (20% EtOAc/Hex, R_f 0.40) afforded **III-45n** as a colorless oil (0.125 g, 15%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.44 (d, *J* = 7.9 Hz, 1H), 7.55 – 7.47 (m, 3H), 7.43 – 7.28 (m, 4H), 7.23 – 7.16 (m, 2H), 3.56 (dd, *J* = 7.5, 5.6 Hz, 1H), 3.52 (s, 3H), 2.25 (d, *J* = 1.3 Hz, 3H), 2.15 (dd, *J* = 7.3, 5.7 Hz, 1H), 1.92 (dd, *J* = 9.2, 5.7 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.3, 164.6, 135.9, 135.4, 131.6, 129.0, 127.7, 126.0, 125.7, 124.0, 121.1, 119.7, 119.0, 116.6, 53.1, 39.8, 28.2, 20.0, 9.7. **IR:** 3080.6 (w), 2939.6 (w), 2896.9 (w), 1724.3 (s), 1657.6 (s), 1421.8 (s), 1382.7 (s), 1267.7 (s), 789.5 (s), 664.3 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 365.1079, Obs. 365.1083.

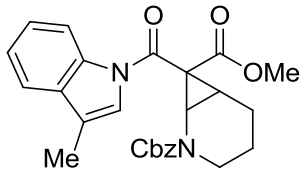


Methyl 6-(3-methyl-1*H*-indole-1-carbonyl)-2-oxabicyclo[3.1.0]hexane-6-carboxylate (III-45o): The general procedure was followed using 2,3-dihydrofuran (0.073 g, 1.05 mmol), methyl 2-diazo-3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.350 g, 1.36 mmol), Rh_2esp_2 (1.0 mg, 1.31 μmol), and DCM (9 mL). After 10 h, the reaction was quenched and column chromatography (20% EtOAc/Hex, R_f 0.30) afforded **III-45o** as a brown solid (0.235 g, 75%). [**m.p.** 83-85 °C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.72 – 7.63 (m, 1H), 7.56 – 7.49 (m, 2H), 7.31 – 7.17 (m, 2H), 6.27 (d, *J* = 6.2 Hz, 1H), 4.19 – 4.10 (m, 1H), 4.05 – 3.97 (m, 1H), 3.96 – 3.85 (m, 1H), 3.72 (s, 3H), 2.35 (s, 3H), 2.25 – 2.16 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 164.1, 156.4, 135.8, 130.3, 125.0, 123.2, 121.7, 118.8, 115.2, 114.2, 108.3, 89.2, 67.1, 50.9, 47.3, 32.0, 9.5. **IR**: 2951.9 (w), 2880.5 (w), 1740.9 (s), 1691.3 (s), 1599.3 (w), 1449.2 (s), 1348.9 (s), 1105.2 (s), 1064.3 (s), 995.6 (s), 734.8 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 299.1158, Obs. 299.1155.

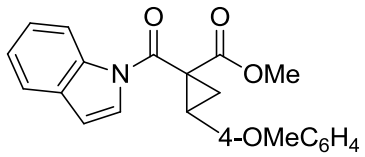


Methyl 7-(3-methyl-1*H*-indole-1-carbonyl)-2-oxabicyclo[4.1.0]heptane-7-carboxylate (III-45p): The general procedure was followed using 2,3-dihydropyran (95 μL, 1.04 mmol), methyl 2-diazo-3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.350 g, 1.36 mmol), Rh_2esp_2 (1.0 mg, 1.31 μmol), and DCM (8 mL). After 12 h, the reaction was quenched, and column chromatography (20% EtOAc/Hex, R_f 0.40) afforded **III-45p** as a pale red solid (0.142 g, 43%). [**m.p.**123-125 °C]. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.45 (d, *J* = 8.1 Hz, 1H), 7.51 – 7.43 (m, 1H), 7.42 – 7.22 (m, 2H), 7.17 (s, 1H), 6.54 (s, 1H), 4.60 (s, 1H), 4.00 – 3.87 (m, 2H), 3.77 (s, 3H), 2.39 – 2.27 (m, 1H), 2.26 (s, 3H), 2.14 – 2.02

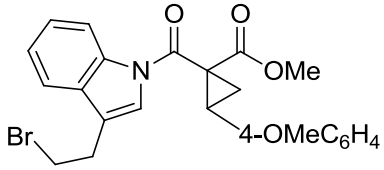
(m, 1H), 1.97 – 1.77 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.8, 165.6, 144.5, 136.0, 131.2, 125.3, 123.8, 121.1, 119.2, 118.7, 116.7, 106.4, 80.7, 65.6, 56.0, 52.6, 21.8, 21.5, 9.6. **IR**: 2942.4 (w), 2866.2 (w), 1756.5 (s), 1694.6 (s), 1651.7 (s), 1608.9 (w), 1451.7 (s), 1385.0 (s), 1349.3 (s), 1140.7 (s), 1065.9 (s), 1018.3 (m), 937.4 (m), 745.4 9 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 313.1314, Obs. 313.1312.



2-Benzyl 7-methyl 7-(3-methyl-1*H*-indole-1-carbonyl)-2-azabicyclo[4.1.0]heptane-2,7-dicarboxylate (III-45q). The general procedure was followed using benzyl 3,4-dihydropyridine-1(2*H*)-carboxylate (0.179 g, 0.897 mmol), methyl 2-diazo-3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.300 g, 1.17 mmol), Rh_2esp_2 (1.3 mg, 1.79 μmol), and DCM (9 mL). After 12 h, the reaction was quenched, and column chromatography (20% EtOAc/Hex, R_f 0.25) afforded **III-45q** as a colorless oil (0.295 g, 74%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.48 (d, *J* = 7.9 Hz, 1H), 7.49 (d, *J* = 7.5 Hz, 1H), 7.42 – 7.26 (m, 6H), 7.13 (t, *J* = 32.4 Hz, 2H), 5.20 (s, 2H), 4.77 (d, *J* = 26.5 Hz, 1H), 3.76 (d, *J* = 11.9 Hz, 3H), 3.71 – 3.44 (m, 2H), 2.27 (s, 3H), 2.51 – 2.02 (m, 2H), 1.96 – 1.74 (m, 2H). **^{13}C NMR** (75 MHz,$CDCl_3$) δ 168.5, 165.4, 153.4, 152.6, 135.9, 135.8, 131.2, 128.4, 128.1, 128.0, 126.2, 125.7, 125.4, 123.8, 121.1, 119.3, 118.7, 116.7, 111.5, 110.8, 67.6, 57.5, 52.7, 41.9, 41.7, 23.5, 22.8, 21.1, 14.5, 9.6. **IR**: 2942.4 (w), 2880.5 (w), 1751.6 (w), 1703.3 (s), 1691.6 (s), 1449.2 (m), 1406.5 (m), 1319.9 (m), 1260.5 (m), 1172.1 (m), 747.1 (m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 446.1842, Obs. 446.1840.

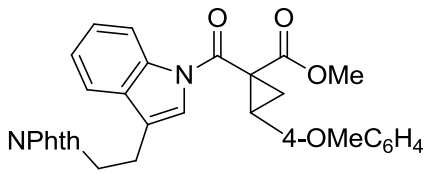


Methyl 1-(1*H*-indole4-1-carbonyl)-2-(4-methoxyphenyl)cyclopropanecarboxylate (III-45r): The general procedure was followed using 4-methoxystyrene (0.061 g, 0.459 mmol) methyl 2-diazo-3-(5-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.331 g, 2.466 mmol), Rh_2esp_2 (1.87 mg, 2.4 μmol), and DCM (20 mL). After 12 h, the reaction was quenched, and column chromatography (20% EtOAc/Hex, R_f 0.30) afforded **III-45r** as a white solid (0.625 g, 72.8%). [**m.p.** 83-85 °C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.44 (d, *J* = 8.2 Hz, 1H), 7.56 – 7.46 (m, 2H), 7.39 – 7.19 (m, 4H), 6.86 – 6.80 (m, 2H), 6.63 – 6.60 (m, 1H), 3.76 (s, 3H), 3.44 – 3.34 (m, 4H), 2.38 (dd, *J* = 8.3, 5.3 Hz, 1H), 1.82 (dd, *J* = 9.7, 5.6, 0.7 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.8, 166.2, 158.9, 135.7, 130.4, 130.1, 125.8, 125.2, 124.7, 124.0, 120.9, 116.4, 113.5, 109.7, 55.1, 52.7, 39.3, 31.2, 18.8. **IR**: 3109.7 (w), 3010.1 (w), 2947.0 (w), 2827.4 (w), 1741.56 (m), 1715.0 (s), 1685.1 (s), 1615.4 (m), 1505.8 (m), 1450.0 (s), 1376.29 (m), 1333.4 (s), 1306.6 (s), 1246.1 (s), 1160.6 (s), 1149.4 (s), 1123.91 (m), 1074.1 (m), 1030.9 (m), 951.2 (m), 841.7(m), 747.6 (s), 629.1 (m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 349.1314, Obs. 349.1310.



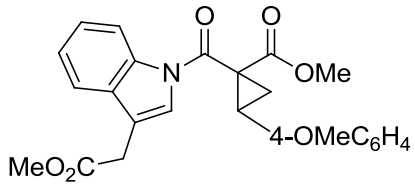
Methyl 1-(3-(2-bromoethyl)-1*H*-indole-1-carbonyl)-2-(4-methoxyphenyl) cyclopropanecarboxylate (III-45s): The general procedure was followed using 4-methoxy styrene (0.073 g, 0.549 mmol), methyl 3-(3-(2-bromoethyl)-1*H*-indol-1-yl)-2-diazo-3-oxopropanoate (0.250 g, 0.713 mmol), Rh_2esp_2 (1.0 mg, 1.31 μmol), and DCM

(15 mL). After 12 h, the reaction was quenched, and column chromatography (20% EtOAc/Hex, R_f 0.35) afforded **III-45s** as a white solid (0.188 g, 75%). [**m.p.** 122-124 ^oC]. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.43 (d, *J* = 8.1 Hz, 1H), 7.51 – 7.45 (m, 1H), 7.41 – 7.19 (m, 5H), 6.86 – 6.79 (m, 2H), 3.76 (s, 3H), 3.61 (t, *J* = 7.0 Hz, 2H), 3.42 – 3.34 (m, 4H), 3.23 (t, *J* = 7.3, 4.4 Hz, 2H), 2.38 (dd, *J* = 8.3, 5.3 Hz, 1H), 1.82 (dd, *J* = 9.4, 5.2 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.8, 166.0, 158.9, 136.0, 130.1, 130.0, 126.0, 125.6, 124.0, 122.4, 120.1, 119.3, 118.5, 116.7, 113.6, 55.2, 52.8, 43.4, 39.3, 31.4, 31.3, 28.7, 18.9. **IR**: 2982.4 (w), 2917.1 (w), 1722.1 (s), 1658.4 (s), 1441.3 (s), 1375.7 (s), 934.5 (s), 700.5 (s), 662.9 (m) cm^{-1}. **HRMS (ESI) M/Z+** Calc. 455.0708, Obs. 455.0732.

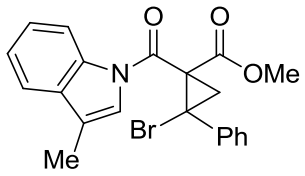


Methyl 1-(3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-1*H*-indole-1-carbonyl)-2-(4-methoxy phenyl)cyclopropanecarboxylate (III-45t): The general procedure was followed using 4-methoxystyrene (0.208 g, 1.55 mmol), methyl 3-(3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-1*H*-indol-1-yl)-3-oxopropanoate (0.810 g, 1.95 mmol), Rh_2esp_2 (1.3 mg, 1.71 μmol), and DCM (8 mL). After 12 h, the reaction was quenched, and column chromatography (40% EtOAc/Hex, R_f 0.38) afforded **III-45t** as a pale brown solid (0.182 g, 23%). [**m.p.** 158-160 ^oC] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.44 (d, *J* = 7.9 Hz, 1H), 7.88 – 7.81 (m, 2H), 7.78 – 7.65 (m, 3H), 7.44 – 7.24 (m, 5H), 6.92 – 6.83 (m, 2H), 4.02 (t, *J* = 7.2 Hz, 2H), 3.81 (s, 3H), 3.39 (t, J = 9.0, 1H), 3.38 (s, 3H), 3.11 (t, *J* = 7.7 Hz, 2H), 2.41 (dd, *J* = 8.3, 5.3 Hz, 1H), 1.79 (dd, *J* = 9.4, 5.3 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) (Rotamers!!) δ 168.2, 167.7, 166.0, 158.9, 136.1, 134.0, 133.8, 132.0, 130.4, 130.2, 126.0, 125.6, 124.0,

123.3, 123.2, 122.1, 122.0, 119.6, 119.5, 119.0, 118.9, 116.6, 113.6, 55.2, 53.4, 52.7, 39.6, 38.5, 37.4, 31.3, 24.3, 18.9. **IR**: 3051.9 (w), 2942.4 (w), 1760.0 (w), 1708.8 (s), 1685.1 (s), 1594.6 (m), 1513.6 (m), 1442.2 (m), 1375.5 (m), 1242.2 (m), 1104.0 (w), 832.6 (m), 732.8 (s), cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 522.1791, Obs. 522.1777.



Methyl 1-(3-(2-methoxy-2-oxoethyl)-1*H*-indole-1-carbonyl)-2-(4-methoxyphenyl) cyclopropanecarboxylate (III-45u): The general procedure was followed using 4-methoxystyrene (0.211 g, 1.57 mmol), methyl 2-diazo-3-(3-(2-methoxy-2-oxoethyl)-1*H*-indol-1-yl)-3-oxopropanoate (0.611 g, 1.94 mmol,), Rh_2esp_2 (1.5 mg, 1.98 μmol), and DCM (8 mL). After 14 h, the reaction was quenched, and column chromatography (EtOAc/Hex, R_f 0.21) afforded **III-45u** as a yellow solid (0.312 g, 47%). [**m.p.** 82-84 ^oC]. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.46 (d, *J* = 8.1 Hz, 1H), 7.58 – 7.49 (m, 2H), 7.46 – 7.26 (m, 4H), 6.92 – 6.82 (m, 2H), 3.81 (s, 3H), 3.73 (s, 2H), 3.73 (s, 3H), 3.43 (s, 3H), 3.43 (t, J = 4.5 Hz, 1H), 2.42 (dd, *J* = 8.3, 5.3 Hz, 1H), 1.86 (dd, *J* = 9.4, 5.2 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.0, 167.8, 166.0, 158.9, 135.9, 130.2, 130.1, 125.9, 125.6, 124.0, 123.3, 119.0, 116.6, 115.7, 113.6, 55.2, 52.8, 52.2, 39.3, 31.3, 30.8, 18.9. **IR**: 3009.0 (w), 2947.1 (w), 1742.2 9 (s), 1694.6 (s), 1608.9 (m), 1504.1 (m), 1446.9 (s), 1356.5 (s), 1246.9 (s), 1032.6 (m), 827.8 (m), 732.8 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 421.1525, Obs. 421.1519.



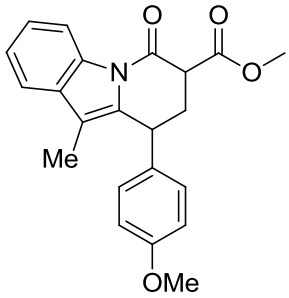
Methyl 2-bromo-1-(3-methyl-1*H*-indole-1-carbonyl)-2-phenylcyclopropane carboxylate (III-45v): The general procedure was followed using (1-bromovinyl)benzene (0.150 g, 0.819 mmol), methyl 2-diazo-3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.274 g, 1.065 mmol), Rh_2esp_2 (1.0 mg, 1.319 μmol), and DCM (12 mL). After 12 h, the reaction was quenched, and column chromatography (20% EtOAc/Hex, R_f 0.40) afforded **III-45v** as a white solid (0.075 g, 22.2%). [**m.p.** 132-134 ^oC] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.12 – 8.04 (m, 1H), 7.48 – 7.37 (m, 3H), 7.27 – 7.18 (m, 3H), 7.17 – 7.04 (m, 3H), 3.80 (s, 3H), 2.86 (d, *J* = 7.3 Hz, 1H), 2.56 (d, *J* = 7.3 Hz, 1H), 2.27 (d, *J* = 1.3 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.76, 161.38, 136.52, 135.61, 131.27, 128.86, 128.57, 127.85, 125.06, 123.77, 122.47, 118.71, 118.60, 116.25, 53.54, 43.79, 40.49, 26.14, 9.70. **IR**: 3066.5 (w), 2960.3 (w), 2920.4 (w), 2867.3 (w), 1737.9 (m), 1691.2 (m), 1678.5 (m), 1612.1 (w), 1448.6 (m), 1388.6 (m), 1346.9 (s), 1238.1 (s), 1218.1 (m), 1146.1 (m), 1120.2 (s), 1063.0 (m), 1018.9 (m), 914.7 (w), 749.3 (s), 693.5 (s), 632.5 (w) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 411.0470, Obs. 411.0461.

3.5.2.4. In(OTf)$_3$-Catalyzed Homo-Nazarov Cyclizations

General Method A: The cyclopropyl β-amide ester **III-45** (1.0 equiv.) was added to a solution of $In(OTf)_3$ (0.30 equiv.) in anhydrous dichloromethane (2 mL) at room temperature. Upon completion, the reaction mixture was quenched with water and the product was extracted from the aqueous phase with dichloromethane. The combined

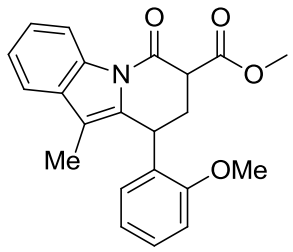
organic layers were washed with brine and dried over $MgSO_4$. The organic layers were concentrated for silica gel flash column chromatography.

General Method B: To a mixture of $In(OTf)_3$ (0.30 equiv.) in anhydrous 1,2-dichloroethane heated to a reflux, dissolved cyclopropyl β-amide ester **III-45** (1.0 equiv.) was syringed into the reaction vessel. The reaction was monitored by TLC and quenched with water. The phases were separated, and the product was extracted from the aqueous phase with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated for silica gel flash column chromatography.



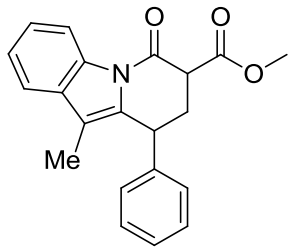
Methyl 9-(4-methoxyphenyl)-10-methyl-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-7-carboxylate(III-46a): Methyl 2-(4-methoxyphenyl)-1-(3-methyl-1*H*-indole-1-carbonyl)cyclopropanecarboxylate (0.100 g, 0.275 mmol), $In(OTf)_3$ (0.046 g, 0.082 mmol) and DCM (4 mL) were combined according to general method A to afford **III-46a** as a pale brown oil (0.099 g, 99%) after 2 h. R_f 0.35 (20% EtOAc/Hex). *Diastereomeric ratio*: (2.6:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.55 – 8.47 (m, 1.34), 7.50 – 7.28 (m, 4.53), 7.15 – 7.09 (m, 0.86), 7.01 – 6.95 (m, 2.09), 6.88 – 6.80 (m, 3.05), 4.59 (t, *J* = 4.3 Hz, 0.94), 4.34 (dd, *J* = 8.5, 5.1 Hz, 0.36), 3.81 – 3.78 (m, 8.28), 3.69 (d, *J* = 4.5 Hz, 0.56), 3.65 (d, *J* = 4.5 Hz, 0.56), 3.56 (d, *J* = 1.1 Hz, 1.37), 2.92 – 2.68 (m, 1.40), 2.59 – 2.34 (m, 1.39), 2.00 (s, 3.0), 1.75 (s, 1.26). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.6, 169.2, 165.0, 164.9, 158.5, 158.5, 134.5, 134.4, 133.7, 133.5, 132.8, 132.3, 131.3, 131.0, 128.9, 128.3,

124.8, 124.8, 124.1, 124.0, 118.1, 118.0, 116.5, 115.2, 114.8, 114.1, 113.9, 55.1, 52.5, 52.4, 49.7, 47.1, 43.4, 37.9, 35.2, 33.8, 33.0, 8.7, 8.3. **IR**: 3051.9 (w), 2932.8 (w), 1747.0 (s), 1685.1 (s), 1618.4 9 (w), 1451.7 (s), 1366.0 (s), 1242.2 (s), 1170.7 (s), 1156.4 (s), 1023.1 (s), 899.2 (m), 729.0 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 363.1471, Obs. 363.1475.

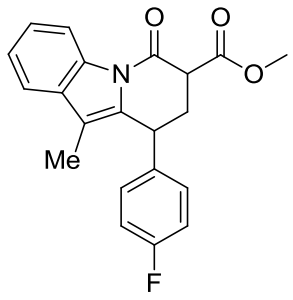


Methyl 9-(2-methoxyphenyl)-10-methyl-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*] indole-7-carboxylate (III-46b): Methyl 2-(2-methoxyphenyl)-1-(3-methyl-1*H*-indole-1-carbonyl)cyclopropanecarboxylate (0.070 g, 0.192 mmol), $In(OTf)_3$ (0.032 g, 0.057 mmol) and DCM (3 mL) were mixed according to general method A to afford **III-46b** as a pale yellow oil (0.066 g, 95.0%) after 3 h. R_f 0.37 (20% EtOAc/Hex). *Diastereomeric ratio*: (3.2:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.59 – 8.48 (m, 1.32), 7.50 – 7.29 (m, 4.33), 7.28 – 7.19 (m, 1.66), 6.93 (dd, *J* = 8.3, 3.2 Hz, 1.57), 6.84 – 6.74 (m, 1.84), 6.57 (dd, *J* = 7.5, 1.6 Hz, 1.12), 4.95 (dd, *J* = 4.9, 3.0 Hz, 1.03), 4.80 (t, *J* = 6.1 Hz, 0.32), 3.97 – 3.88 (m, 4.23), 3.83 – 3.75 (m, 3.52), 3.74 – 3.62 (m, 1.07), 3.45 (s, 0.94), 2.95 (dt, *J* = 13.8, 7.0 Hz, 0.37), 2.81 – 2.66 (m, 1.36), 2.61 – 2.44 (m, 1.44), 2.31 (q, *J* = 7.8 Hz, 0.37), 2.00 (s, 2.89), 1.81 (s, 0.94). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.9, 169.4, 165.5, 156.8, 156.5, 134.6, 134.0, 131.2, 129.0, 128.6, 128.5, 128.4, 128.3, 124.7, 124.66, 124.15, 124.0, 122.1, 120.5, 120.4, 118.2, 117.9, 116.7, 116.6, 114.4, 110.5, 110.3, 55.4, 55.3, 52.5, 52.3, 49.5, 47.6, 31.0, 30.7, 30.1, 8.3, 8.3. **IR**: 3097.4 (w), 2986.9 (w), 2854.2 (w),

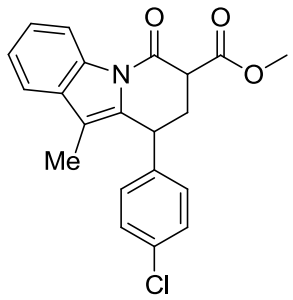
1724.1 (s), 1711.7 (m), 1657.3 (s), 1591.8 (m), 1440.0(s), 1374.7(s), 1221.0(s), 1044.7(s), 784.2 (s), 674.3 (m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 363.1471, Obs. 363.1472.



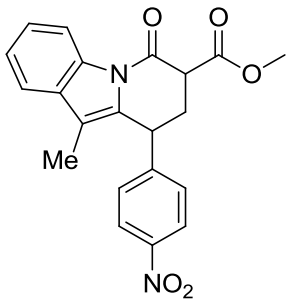
Methyl 10-methyl-6-oxo-9-phenyl-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-7-carboxylate (III-46c): Methyl 1-(3-methyl-1*H*-indole-1-carbonyl)-2-phenylcyclopropane carboxylate (0.100 g, 0.300 mmol), $In(OTf)_3$ (0.050 g, 0.090 mmol) and DCE (4 mL) were combined according to general method B to afford **III-46c** as a brown oil (0.051 g, 52%) after 8 h. R_f 0.25 (20% EtOAc/Hex). *Diastereomeric ratio*: (2.6:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.57 – 8.47 (m, 1.37), 7.53 – 7.27 (m, 10.63), 7.07 (d, *J* = 7.4 Hz, 2.24), 4.64 (t, *J* = 4.3 Hz, 1.00), 4.40 (dd, *J* = 8.2, 5.7 Hz, 0.39), 3.80 (dd, *J* = 9.4, 3.3 Hz, 3.61), 3.75 – 3.63 (m, 1.46), 3.53 (d, *J* = 1.1 Hz, 1.28), 2.95 – 2.74 (m, 2.28), 2.64 – 2.42 (m, 2.12), 2.00 (s, 3.13), 1.74 (s, 1.24). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.6, 169.2, 165.0, 164.9, 140.8, 140.5, 134.6, 133.3, 133.2, 131.3, 131.1, 128.9, 128.7, 128.6, 128.3, 128.0, 127.6, 127.3, 127.2, 127.2, 125.7, 125.0, 124.2, 124.1, 118.2, 118.0, 116.7, 116.6, 115.47, 115.12, 52.6, 52.4, 49.8, 47.1, 38.7, 36.1, 33.8, 32.9, 8.8, 8.4. **IR**: 3032.9 (w), 2961.4 (w), 2904.3 (w), 1744.6 (s), 1699.4 (s), 1537.4 (w), 1457.6 (s), 1382.5 (s), 1242.2 (m), 1018.3 (w), 749.9 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 333.1365, Obs. 333.1367.



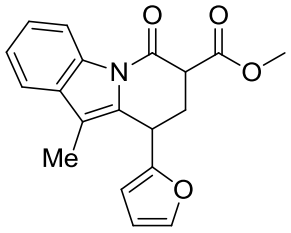
Methyl 9-(4-fluorophenyl)-10-methyl-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-7-carboxylate (III-46d): Methyl 2-(4-fluorophenyl)-1-(3-methyl-1*H*-indole-1-carbonyl) cyclopropanecarboxylate (0.100 g, 0.285 mmol), $In(OTf)_3$ (0.047 g, 0.085 mmol, 30 mol%) and DCE (4 mL) were combined according to general method B to afford **III-46d** as a brown oil (0.048 g, 48%) after 8 h. R_f 0.28 (20% EtOAc/Hex). *Diastereomeric ratio*: (2.6:1). **^{1}H NMR** (300 MHz, CDCl3) δ 8.57 – 8.46 (m, 1.37), 7.76 (d, *J* = 8.1 Hz, 0.68), 7.53 – 7.29 (m, 5.16), 7.26 – 6.77 (m, 12.82), 5.75 (s, 0.62), 4.62 (t, *J* = 4.4 Hz, 1.00), 4.39 (dd, *J* = 8.2, 5.3 Hz, 0.35), 3.80 (s, 3.03), 3.65 (dd, *J* = 11.8, 4.5 Hz, 1.24), 3.55 (s, 1.24), 2.93 – 2.79 (m, 2.17), 2.61 – 2.38 (m, 1.87), 2.00 (s, 3.18), 1.76 (s, 1.43). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.5, 169.2, 164.8, 160.2, 136.2, 134.6, 132.9, 131.0, 129.6, 129.4, 128.9, 128.8, 125.1, 124.3, 124.2, 118.3, 118.1, 116.6, 115.9, 115.6, 115.4, 115.2, 52.7, 52.5, 49.6, 47.8, 47.1, 35.9, 35.4, 33.8, 33.0, 33.1, 8.4. **IR**: 3051.9 (w), 2932.8 (w), 2861.4 (w), 1738.3 (m), 1664.6 (m), 1604.1 (m), 1535.1 (m), 1508.3 (m), 1314.8 (m), 1250.8 (s), 1209.5 (s), 1097.4 (m), 989.0 (w), 832.4 (m), 736.0 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 351.1271, Obs. 351.1272.



Methyl 9-(4-chlorophenyl)-10-methyl-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-7-carboxylate (III-46e): Methyl 2-(4-chlorophenyl)-1-(3-methyl-1*H*-indole-1-carbonyl) cyclopropanecarboxylate (0.100 g, 0.272 mmol), $In(OTf)_3$ (0.045 g, 0.081 mmol) and DCE (4 mL) were mixed according to general method B to yield **III-46e** as a brown oil (0.049 g, 49.7%) after 12 h. R_f 0.43 (15% EtOAc/Hex). *Diastereomeric ratio*: (1.9:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.55 – 8.46 (m, 1.38), 7.50 – 7.27 (m, 8.02), 7.17 – 7.13 (m, 1.05), 7.04 – 6.98 (m, 2.15), 6.81 – 6.77 (m, 0.45), 4.61 (t, *J* = 4.6 Hz, 1.00), 4.40 (dd, *J* = 7.6, 5.8 Hz, 0.52), 3.80 (s, 3.14), 3.65 (d, *J* = 4.5 Hz, 0.55), 3.61 (d, *J* = 4.5 Hz, 0.55), 3.54 (s, 1.24), 2.93 – 2.70 (m, 2.53), 2.62 – 2.37 (m, 2.54), 1.99 (s, 2.80), 1.77 (s, 1.20). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.4, 164.7, 139.1, 134.6, 133.2, 132.6, 131.0, 129.3, 129.1, 129.0, 128.8, 128.7, 127.1, 125.2, 124.4, 124.3, 118.3, 118.2, 116.7, 115.3, 77.4, 77.2, 77.0, 76.5, 52.7, 52.5, 49.6, 47.1, 38.0, 35.6, 33.6, 32.9, 8.9, 8.5. **IR**: 3051.9 (w), 2956.6 (m), 2918.6 (m), 2847.1 (m), 1747.0 (m), 1699.4 (m), 1613.6 (m), 1542.2 (s), 1313.6 (m), 1251.5 (m), 1208.8 (m), 1094.5 (w), 1004.0 (w), 832.6 (w), 737.7 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 367.0975, Obs. 367.0988.

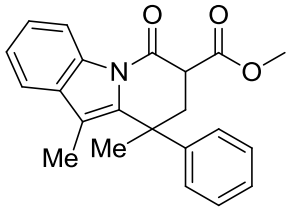


Methyl 10-methyl-9-(4-nitrophenyl)-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-7-carboxylate (III-46f): Methyl 1-(3-methyl-1*H*-indole-1-carbonyl)-2-(4-nitrophenyl) cyclopropanecarboxylate (0.100 g, 0.264 mmol), $In(OTf)_3$ (0.044 g, 0.079 mmol) and DCE (4 mL) were mixed according to general method B to yield a brown oil after 20 h. The reaction afforded an inseparable mixture of trace amounts of **III-46f** and other by-products as observed by crude ^{1}H NMR. R_f 0.35 (15% EtOAc/Hex).



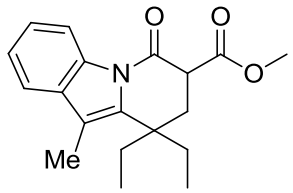
Methyl 9-(furan-2-yl)-10-methyl-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-7-carboxylate (III-46g): Methyl 2-(furan-2-yl)-1-(3-methyl-1*H*-indole-1-carbonyl)cyclopropane carboxylate (0.050 g, 0.154 mmol), $In(OTf)_3$ (0.026 g, 0.046 mmol) and DCM (3 mL) were mixed according to general method A to afford **III-46g** as a colorless oil (0.049 g, 99.0%) after 2 h. R_f 0.40 (20% EtOAc/Hex). *Diastereomeric ratio*: (4.5:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.57 – 8.51 (m, 0.37), 8.50 – 8.42 (m, 0.97), 7.53 – 7.46 (m, 1.50), 7.42 – 7.29 (m, 3.77), 6.30 – 6.25 (m, 1.21), 5.91 – 5.87 (m, 1.16), 4.65 (t, *J* = 3.9 Hz, 1), 4.52 (t, *J* = 5.2 Hz, 0.22), 3.84 (d, *J* = 1.0 Hz, 3.24), 3.81 – 3.72

(m, 1.42), 3.51 (d, *J* = 0.8 Hz, 0.69), 3.08 (dt, *J* = 13.8, 5.6 Hz, 0.25), 2.72 (dt, *J* = 4.4, 3.6 Hz, 2.07), 2.53 (dt, *J* = 13.8, 5.3 Hz, 0.27), 2.15 (d, *J*= 0.3 Hz, 3.09), 2.00 (d, *J* = 0.9 Hz, 0.67). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.6, 164.8, 152.4, 142.4, 142.1, 134.6, 131.1, 130.8, 125.1, 124.2, 118.3, 116.6, 115.3, 110.3, 110.2, 108.1, 107.6, 52.7, 47.7, 31.3, 30.7, 29.3, 8.3. **IR**: 3090.2 (w), 2936.8 (w), 1767.1 (s), 1725.6 (s), 1469.4(s), 1376.2(m), 1269.5(m), 785.4 (s), 663.0 (m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 323.1158, Obs. 323.1159.

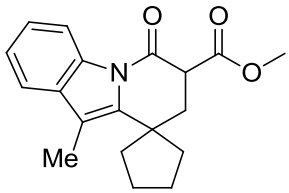


Methyl 9,10-dimethyl-6-oxo-9-phenyl-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-7-carboxylate (III-46h): Methyl 2-methyl-1-(3-methyl-1*H*-indole-1-carbonyl)-2-phenyl cyclopropanecarboxylate (0.070 g, 0.201 mmol), $In(OTf)_3$ (0.033 g, 0.060 mmol) and DCM (3 mL) were combined according to general Method A to afford a **III-46h** as a white solid (0.065 g, 94.14%) after 2 h. R_f 0.28 (20% EtOAc/Hex). [**m.p.** 139-141 ^oC] *Diastereomeric ratio*: (1.1:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.58 – 8.50 (m, 1.81), 7.54 (ddt, *J* = 7.6, 4.3, 2.2 Hz, 1.0), 7.45 – 7.25 (m, 13.52), 7.13 – 7.08 (m, 2.11), 3.99 (dd, *J* = 12.2, 5.0 Hz, 0.80), 3.80 (s, 3.0), 3.72 (s, 2.71), 3.43 (dd, *J* = 13.2, 4.4 Hz, 0.99), 2.84 (dt, *J* = 26.7, 13.4 Hz, 1.88), 2.50 – 2.41 (m, 1.35), 2.26 – 2.18 (m, 4.15), 1.99 (s, 2.99), 1.85 (s, 2.62), 1.65 (s, 2.68). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.5, 169.4, 165.3, 164.9, 145.9, 143.8, 138.5, 136.9, 134.3, 134.2, 131.6, 131.9, 128.9, 128.5, 127.1, 126.8, 126.4, 125.9, 125.1, 124.9, 124.1, 124.1, 118.0, 117.9, 116.7, 115.6, 114.6, 52.6, 48.5, 47.9, 42.1,

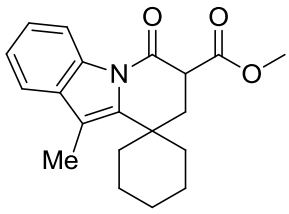
41.23, 40.74, 39.56, 29.4, 24.6, 10.0, 9.2. **IR**: 3040.9 (w), 2963.4 (w), 2890.4 (w), 1722.2 (s), 1640.6 (s), 1483.9 (s), 1383.5 (s), 1270.4 (m), 1182.4 (m), 1134.3 (w), 740.1 (s), 640.4 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 347.1521, Obs. 347.1516.



Methyl 9,9-diethyl-10-methyl-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-7-carboxylate (III-46i): Methyl 2,2-diethyl-1-(3-methyl-1*H*-indole-1-carbonyl)cyclopropane carboxylate (0.055 g, 0.175 mmol), $In(OTf)_3$ (0.029 g, 0.052 mmol) and DCE (3 mL) were mixed according to general method B to yield **III-46i** as a colorless oil (0.046 g, 84.8%) after 6 h. R_f 0.38 (20% EtOAc/Hex). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.51 – 8.44 (m, 1H), 7.44 (ddd, *J* = 6.7, 4.5, 2.6 Hz, 1H), 7.34 – 7.28 (m, 2H), 3.94 – 3.83 (m, 4H), 2.58 (t, *J* = 13.5 Hz, 1H), 2.30 (d, *J* = 0.7 Hz, 3H), 2.21 (dt, *J* = 14.6, 7.4 Hz, 1H), 1.95 (dd, *J* = 13.7, 5.0 Hz, 1H), 1.87 – 1.65 (m, 3H), 0.93 (dt, *J* = 10.0, 7.4 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.2, 165.3, 136.9, 134.4, 131.7, 124.7, 123.9, 117.6, 116.6, 113.7, 77.4, 76.9, 76.5, 52.7, 47.4, 39.3, 32.3, 31.6, 29.1, 9.7, 8.5, 8.3. **IR**: 3025.9 (w), 2894.8 (w), 1786.6 (s), 1725.4 (s), 1484.2 (s), 1383.2 (m), 1283.0 (m), 1180.6 (m), 713.41 (s), 662.9 (m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 313.1678, Obs. 313.1678.

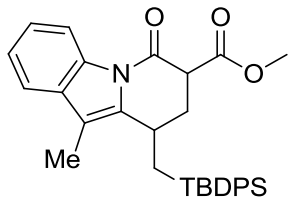


Methyl 10'-methyl-6'-oxo-7',8'-dihydro-6'*H*-spiro[cyclopentane-1,9'-pyrido[1,2-*a*]indole]-7'-carboxylate (III-46j): Methyl 1-(3-methyl-1*H*-indole-1-carbonyl)spiro[2.4] heptane-1-carboxylate (0.050 g, 0.160 mmol), $In(OTf)_3$ (0.027 g, 0.048 mmol) and DCE (3 mL) were mixed according to general method B to yield **III-46j** as a colorless oil (0.044 g, 88.8%) after 6 h. R_f 0.35 (20% EtOAc/Hex). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.48 – 8.41 (m, 1H), 7.47 – 7.41 (m, 1H), 7.30 (ddd, *J* = 4.6, 4.2, 2.9 Hz, 2H), 3.85 (d, *J* = 0.8 Hz, 3H), 3.84 – 3.79 (m, 1H), 2.69 – 2.54 (m, 1H), 2.47 (t, *J* = 13.2 Hz, 1H), 2.30 (d, *J* = 0.7 Hz, 3H), 2.13 (dd, *J* = 13.4, 4.6 Hz, 1H), 2.02 – 1.83 (m, 5H), 1.83 – 1.70 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.9, 165.4, 139.3, 134.0, 131.9, 124.7, 124.0, 117.6, 116.5, 112.6, 52.7, 48.8, 42.6, 39.0, 38.7, 37.8, 25.8, 25.3, 9.73. **IR**: 2998.5 (w), 2893.7 (w), 1786.8 (s), 1724.9 (s), 1470.0 (s), 1385.1 (m), 1269.5 (m), 1180.4 (m), 714.3 (s), 662.7 (m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 311.1521, Obs. 311.1520.



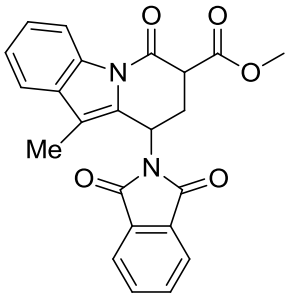
Methyl 10'-methyl-6'-oxo-7',8'-dihydro-6'*H*-spiro[cyclohexane-1,9'-pyrido[1,2-*a*]indole]-7'-carboxylate (III-46k): Methyl 1-(3-methyl-1*H*-indole-1-carbonyl)spiro[2.5]octane-1-carboxylate (0.080 g, 0.246 mmol), $In(OTf)_3$ (0.041 g, 0.073

mmol) and DCE (3 mL) were mixed according to general method B to yield **III-46k** as a colorless oil (0.062 g, 78.6%) after 6 h. R_f 0.39 (20% EtOAc/Hex). *(Conformers!!)* **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.49 – 8.41 (m, 1H), 7.47 – 7.42 (m, 1H), 7.36 – 7.27 (m, 2H), 3.86 (dd, *J* = 2.9, 0.6 Hz, 3H), 3.76 (dd, *J* = 13.1, 4.6 Hz, 1H), 2.71 – 2.59 (m, 3H), 2.54 – 2.39 (m, 4H), 2.36 – 2.17 (m, 2H), 1.91 – 1.76 (m, 4H), 1.70 (d, *J* = 11.9 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.2, 165.5, 139.5, 134.0, 132.1, 125.1, 124.8, 123.9, 121.7, 119.4, 117.7, 116.6, 114.4, 113.1, 58.6, 52.7, 47.2, 36.1, 35.6, 33.9, 33.7, 32.7, 31.2, 30.8, 25.6, 25.4, 23.1, 21.5, 21.3, 10.8, 10.2. **IR**: 2969.7 (w), 2890.9 (w), 1736.7 (m), 1689.1 (m), 1469.0 (m), 1382.7 (m), 1269.5 (s), 759.9 (s), 662.9 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 325.1678, Obs. 325.1681.



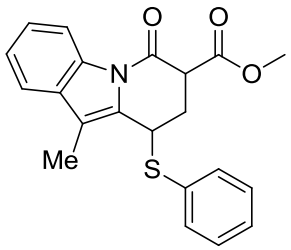
Methyl 9-((*tert*-butyldiphenylsilyl)methyl)-10-methyl-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-7-carboxylate (III-46l): Methyl 2-((*tert*-butyldiphenylsilyl) methyl)-1-(3-methyl-1*H*-indole-1-carbonyl)cyclopropanecarboxylate (0.100 g, 0.196 mmol), $In(OTf)_3$ (0.033 g, 0.058 mmol) and DCE (4 mL) were combined according to general method B to afford **III-46fl** as a colorless oil (0.082 g, 82%) after 16 h. R_f 0.41 (20% EtOAc/Hex). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.37 (ddd, *J* = 4.3, 2.2, 0.6 Hz, 1H), 7.72 – 7.66 (m, 4H), 7.45 – 7.32 (m, 7H), 7.29 – 7.24 (m, 2H), 3.89 (dd, *J* = 13.5, 4.8 Hz, 1H), 3.72 (s, 3H), 3.45 – 3.33 (m, 1H), 2.19 (ddd, *J* = 18.1, 8.8, 3.1 Hz, 1H), 1.99 (s, 3H), 1.83 (ddd, *J* = 13.5, 4.8, 2.5 Hz, 1H), 1.55 (dd, *J* = 8.3, 4.6 Hz, 2H), 1.06 –

1.00 (m, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.7, 165.1, 138.5, 135.8, 135.7, 134.4, 134.1, 133.0, 131.2, 129.5, 129.4, 127.9, 124.5, 124.0, 117.9, 116.5, 112.0, 52.4, 46.7, 29.9, 27.7, 26.5, 18.3, 14.9, 8.5. **IR**: 3061.4 (w), 2951.9 (m), 2928.1 (m), 2851.9 (m), 1745.6 (s), 1692.0 (s), 1457.2 (s), 1381.4 (s), 1270.6 (m), 1103.8 (m), 740.4 (s), 702.1 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 509.2386, Obs. 509.2383.

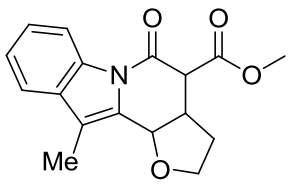


Methyl 9-(1,3-dioxoisoindolin-2-yl)-10-methyl-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-7-carboxylate (III-46m): Methyl 2-(1,3-dioxoisoindolin-2-yl)-1-(3-methyl-1*H*-indole-1-carbonyl) cyclopropane carboxylate (0.090 g, 0.224 mmol), $In(OTf)_3$ (0.037 g, 0.067 mmol) and DCE (4 mL) were mixed according to general method B to yield **III-46m** as a yellow-green solid (0.049 g, 55%) after 8 h. R_f 0.38 (20% EtOAc/Hex). [**m.p.** 167–169^{o}C] *Diastereomeric ratio*: (4.8:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.52 – 8.47 (m, 1.27), 7.89 – 7.70 (m, 5.64), 7.46 – 7.28 (m, 4.18), 5.96 (t, J = 4.5 Hz, 1.00), 4.19 (dt, J = 12.5, 6.3 Hz, 0.70), 3.83 – 3.79 (m, 3.92), 2.86 (ddd, J = 14.1, 11.8, 5.3 Hz, 0.75), 2.58 (ddd, J = 14.3, 4.9, 4.0 Hz, 0.75), 2.29 – 2.26 (m, 0.22), 2.07 (s, 2.75), 2.04 (s, 0.38). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.5, 167.6, 164.4, 134.8, 134.5, 131.3, 130.3, 128.2, 125.8, 124.1, 123.6, 118.5, 116.7, 116.3, 52.8, 48.2, 40.3, 30.7, 8.3. **IR**: 3061.6 (w), 2942.6 (w), 2928.32 (w), 1733.2 (m), 1708.2 (s), 1614.2 (w), 1452.3 (m), 1452.3 (m), 1383.6 (s),

1309.5 (s), 1261.0 (s), 1104.7 (m), 890.4 (m), 734.4 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 402.1216, Obs. 402.1219.

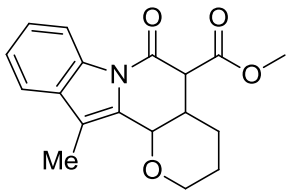


Methyl 10-methyl-6-oxo-9-(phenylthio)-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-7-carboxylate (III-46n): Methyl 1-(3-methyl-1*H*-indole-1-carbonyl)-2-(phenylthio)cyclopropane carboxylate (0.018 g, 0.049 mmol), $In(OTf)_3$ (0.008 g, 0.014 mmol) and DCE (1 mL) were mixed according to general method B to yield **III-46n** as a colorless oil (0.014 g, 81%) after 7 h. R_f 0.30 (20% EtOAc/Hex). *Diastereomeric ratio*: (10:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.54 (d, *J* = 8.6 Hz, 0.10), 8.47 – 8.40 (m, 1), 7.54 – 7.29 (m, 9.0), 4.91 – 4.84 (m, 1.06), 4.48 (dd, *J* = 13.1, 4.8 Hz, 1.04), 3.94 – 3.76 (m, 3.80), 2.72 (td, *J* = 13.6, 3.9 Hz, 1.19), 2.42 – 2.32 (m, 1.42), 2.20 (s, 0.31), 2.04 (s, 3.10). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.6, 164.5, 134.7, 134.5, 132.5, 130.5, 130.4, 129.3, 129.2, 128.8, 128.6, 125.6, 124.3, 118.5, 116.6, 52.8, 46.9, 40.0, 29.6, 8.3. **IR**: 2997.7 (w), 2890.9 (w), 1766.6 (m), 1711.7 (m), 1468.2 (m), 1269.7 (s), 760.1 (s), 663.0 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 365.1119, Obs. 365.1089.



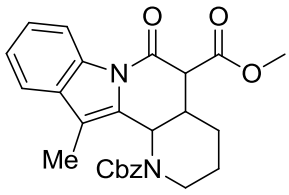
Methyl 11-methyl-5-oxo-2,3,3a,4,5,11b-hexahydrofuro[2',3':3,4]pyrido[1,2-*a*]indole-4-carboxylate (III-46o): Methyl 6-(3-methyl-1*H*-indole-1-carbonyl)-2-oxabicyclo[3.1.0]

hexane-6-carboxylate (0.025 g, 0.083 mmol), $In(OTf)_3$ (0.014 g, 0.025 mmol) and DCM (2 mL) were combined according to general method A to afford **III-46o** as a colorless oil (0.024 g, 97%) after 2.5 h. R_f 0.30 (20% EtOAc/Hex). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.39 (d, *J* = 4.9, 3.3 Hz, 1H), 7.51 (d, *J* = 6.8, 1.3 Hz, 1H), 7.41 – 7.27 (m, 2H), 5.05 (d, *J* = 4.5 Hz, 1H), 4.17 – 3.99 (m, 2H), 3.87 (s, 3H), 3.78 (d, *J* = 10.7 Hz, 1H), 3.32 – 3.21 (m, 1H), 2.47 – 2.22 (m, 1H), 2.32 (s, 3H), 1.96 – 1.82 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.2, 164.0, 134.5, 130.9, 128.8, 125.8, 124.2, 119.5, 118.8, 116.4, 69.9, 66.3, 52.8, 52.3, 40.7, 30.7, 8.5. **IR**: 2947.1 (w), 2923.3 (w), 2856.6 (w), 1744.8 (s), 1703.1 (s), 1623.2 (w), 1459.5 (m), 1382.2 (s), 1265.2 (m), 1035.5 (m), 751.0 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 299.1158, Obs. 299.1158.

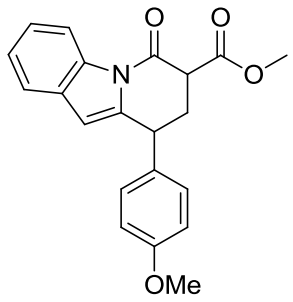


Methyl 12-methyl-6-oxo-3,4,4a,5,6,12b-hexahydro-2*H*-pyrano[2',3':3,4]pyrido[1,2-*a*]indole-5-carboxylate (III-46p): Methyl 7-(3-methyl-1*H*-indole-1-carbonyl)-2-oxabicyclo[4.1.0]heptane-7-carboxylate (0.025 g, 0.079 mmol), $In(OTf)_3$ (0.013 g, 0.023 mmol) and DCM (2 mL) were mixed according to general method A to yield **III-46p** as a pale yellow solid (0.023 g, 92.9%) after 2.5 h. R_f 0.25 (20% EtOAc/Hex). [**m.p.** 128-130^{o}C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.41 (d, 1H), 7.50 (d, 1H), 7.40 – 7.25 (m, 2H), 4.81 (s, 1H), 4.33 (d, *J* = 12.2 Hz, 1H), 4.08 (d, 1H), 3.86 (s, 3H), 3.71 (t, *J* = 11.6, 2.4 Hz, 2H), 2.72 (d, 1H), 2.30 (s, 3H), 1.98 – 1.73 (m, 2H), 1.56 – 1.47 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.5, 165.2, 134.3, 130.8, 125.8, 124.2, 122.2, 118.8, 117.7, 116.6,

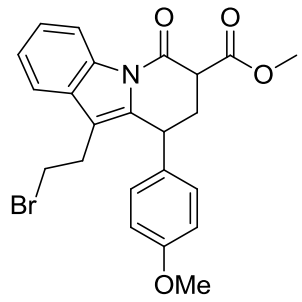
68.3, 68.1, 52.6, 50.1, 35.7, 25.7, 20.4, 8.4. **IR**: 2737.5(w), 1746.9(m), 1632.6(w), 1532.6(m), 1056.8(w), 751.6(s), 680.1(s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 313.1314, Obs. 313.1315.



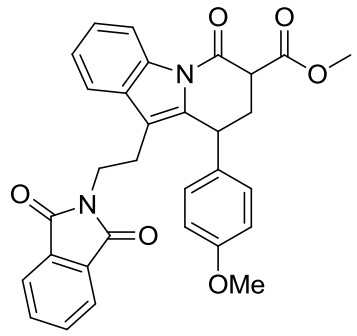
1-Benzyl 5-methyl 12-methyl-6-oxo-2,3,4,4a,5,6-hexahydroindolo[1,2-*h*][1,7] naphthyridine-1,5(12b*H*)-dicarboxylate (III-46q): 2-benzyl 7-methyl 7-(3-methyl-1*H*-indole-1-carbonyl)-2-azabicyclo[4.1.0]heptane-2,7-dicarboxylate (0.100 g, 0.223 mmol), $In(OTf)_3$ (0.037 g, 0.067 mmol) and DCM (4 mL) were combined according to general method A to afford **III-46q** as a colorless oil (0.098 g, 98.0%) after 2 h. R_f 0.25 (25% EtOAc/Hex). *Diastereomeric ratio*: (7.1:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.55 – 8.40 (m, 1.22), 7.52 – 7.27 (m, 10.67), 5.98 (d, 1), 5.91 (d, 0.14), 5.38 – 5.16 (m, 2.64), 4.20 - 4.04 (m, 1.20), 3.95 (dd, *J* = 13.9, 3.7 Hz, 0.23), 3.85 (s, 0.77), 3.74 (s, 3), 3.68 (d, *J* = 1.7 Hz 1.41), 2.81 – 2.50 (m, 2.68), 2.35 – 2.20 (m, 0.32), 2.08 – 2.03 (m, 3.99), 1.79 – 1.85 (m, 1.54), 1.58 – 1.70 (m, 2.70), 1.51 – 1.33 (m, 1.42). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.4, 167.6, 162.6, 155.0, 136.3, 134.5, 131.3, 128.4, 128.3, 128.1, 127.8, 127.7, 125.1, 124.1, 122.0, 117.9, 116.4, 116.3, 67.5, 56.0, 53.5, 53.0, 52.4, 48.3, 39.4, 37.9, 34.5, 31.4, 26.5, 25.1, 24.6, 22.5, 14.6, 7.6. **IR**: 3042.4 (w), 2932.8 (w), 2861.4 (w), 1738.4 (s), 1702.9 (s), 1457.3 (m), 1373.1 (s), 1256.6 (m), 1201.5 (m), 1164.4 (m), 1113.6 (w), 761.1 (m), 689.7 (m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 446.1842, Obs. 446.1840.



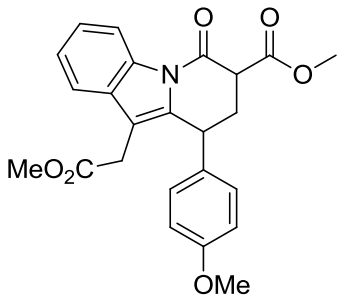
Methyl 9-(4-methoxyphenyl)-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-7-carboxylate (III-46r): Methyl 1-(1*H*-indole-1-carbonyl)-2-(4-methoxyphenyl)cyclopropanecarboxylate **(**0.75 g, 0.215 mmol), $In(OTf)_3$ (0.036 g, 0.064 mmol) and DCM (4 mL) were combined according to general method A to afford **III-46r** as a colorless oil (0.742 g, 98.99%) after 45 min. R_f 0.30 (20% EtOAc/Hex). *Diastereomeric ratio*: (1.1:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.53 – 8.42 (m, 1.77), 7.45 – 7.20 (m, 8.18), 7.19-7.12 (m, 1.68), 6.96 – 6.85 (m, 3.86), 6.08 (s, 0.78), 6.00 – 5.89 (m, 1), 4.36 (dd, *J* = 9.9, 4.2 Hz, 0.76H), 4.13 (dd, *J* = 13.0, 2.6 Hz, 1.09), 3.97 – 3.79 (m, 13.94), 2.79 – 2.64 (m, 1.92), 2.54 – 2.37 (m, 1.88). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.5, 169.3, 165.3, 164.7, 159.1, 158.9, 141.5, 140.6, 135.2, 135.1, 132.7, 132.3, 129.6, 129.5, 129.3, 129.0, 124.7, 124.4, 124.4, 120.1, 120.1, 116.6, 116.5, 114.2, 107.6, 55.3, 53.0, 52.8, 51.6, 49.2, 40.3, 37.4, 33.6, 33.2. IR: 2997.1 (w), 2950.6 (w), 2834.32 (w), 1737.9 (s), 1703.3 (s), 1555.7 (w), 1512.5 (m), 1453.1 (s), 1379.0 (s), 13050.2 (s), 1247.2 (s), 1177.1 (s), 1034.6 (s), 838.4 (m), 798.5 (m), 752.0 (m), 688.9 (w) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 349.1314, Obs. 349.1307.



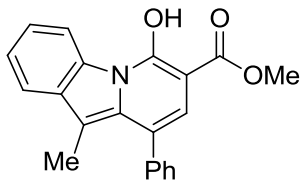
Methyl 10-(2-bromoethyl)-9-(4-methoxyphenyl)-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-7-carboxylate (III-46s): Methyl 1-(3-(2-bromoethyl)-1*H*-indole-1-carbonyl)-2-(4-methoxyphenyl)cyclopropane carboxylate (0.050 g, 0.109 mmol), $In(OTf)_3$ (0.018 g, 0.032 mmol) and DCM (3 mL) were mixed according to general method A to afford **III-46s** as a colorless oil (0.049 g, 98.2%) after 1 h. R_f 0.35 (20% EtOAc/Hex). *Diastereomeric ratio*: (2.7:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.54 (ddd, *J* = 10.3, 6.9, 1.4 Hz, 1.38), 7.53 – 7.29 (m, 4.31), 7.16 – 7.11 (m, 0.81), 6.95 (dd, *J* = 6.9, 4.7 Hz, 2.07), 6.89 – 6.80 (m, 2.88), 4.68 (t, *J* = 4.2 Hz, 1), 4.43 (dd, *J* = 8.8, 5.3 Hz, 0.37), 3.86 – 3.77 (m, 7.57), 3.69 (dd, *J* = 12.2, 4.6 Hz, 1.29), 3.57 (d, *J* = 3.5 Hz, 1.28), 3.53 – 3.05 (m, 4.08), 3.03 – 2.73 (m, 3.37), 2.66 – 2.37 (m, 2.03). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.4, 165.2, 158.8, 135.5, 134.7, 132.3, 129.6, 129.1, 128.3, 125.2, 124.4, 118.0, 116.9, 116.0, 114.3, 114.2, 55.3, 52.7, 47.1, 35.4, 33.0, 30.9, 27.7. **IR**: 3023.9 (w), 2918.9 (w), 1725.1 (s), 1658.6 (s), 1591.0 (m), 1493.2 (s), 1349.0 (m), 993.6(s), 725.0 s), 663.0 (m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 455.0708, Obs. 455.0734.



Methyl 10-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-9-(4-methoxyphenyl)-6-oxo-6,7,8,9-tetrahydro-pyrido[1,2-*a*]indole-7-carboxylate (III-46t): Methyl 1-(3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-1*H*-indole-1-carbonyl)-2-(4-methoxyphenyl)cyclopropane carboxylate (0.050 g, 0.096 mmol), $In(OTf)_3$ (0.016 g, 0.028 mmol) and DCM (3 mL) were mixed according to general method A to yield **III-46t** as a white solid (0.038 g, 76.0%) after 2 h. [**m.p.** 166–168^oC] R_f 0.38 (40% EtOAc/Hex). *Diastereomeric ratio*: (2.8:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.52 – 8.46 (m, 1.35), 7.79 – 7.58 (m, 7.24), 7.41 – 7.26 (m, 2.90), 7.18 – 7.13 (m, 0.89), 7.00 – 6.93 (m, 2.37), 6.86 - 6.72 (m, 2.97), 4.70 (t, *J* = 4.1 Hz, 1), 4.48 (dd, *J* = 8.3, 5.1 Hz, 0.35), 3.85 – 3.80 (m, 0.84), 3.79- 3.63 (m, 11.93), 3.54 (s, 1.09), 3.02 – 2.90 (m, 1.23), 2.88 – 2.71 (m, 3.21), 2.61 – 2.50 (m, 0.57), 2.44 – 2.33 (m, 1.73). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.6, 169.2, 168.0, 165.3, 165.1, 158.8, 158.7, 135.5, 135.3, 134.7, 134.6, 133.8, 132.5, 131.9, 131.9, 130.4, 130.0, 129.1, 128.3, 125.1, 125.0, 124.5, 124.4, 123.1, 123.0, 118.4, 118.2, 116.8, 116.7, 115.7, 115.2, 114.2, 114.1, 55.2, 55.2, 52.7, 52.5, 49.6, 47.0, 37.7, 36.9, 36.8, 35.3, 33.7, 33.2, 23.1, 22.8. **IR**: 3047.1 (w), 2947.1 (w), 2847.1 (w), 1766.03 (w), 1751.74 (m), 1708.8 (s), 1618.4 (m), 1504.1 (m), 1451.7 (m), 1376.6 (s), 1245.9 (s), 1032.6 (s), 837.3 (m), 715.9 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 522.1791, Obs. 522.1791.



Methyl 10-(2-methoxy-2-oxoethyl)-9-(4-methoxyphenyl)-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-7-carboxylate (III-46u): Methyl 1-(3-(2-methoxy-2-oxoethyl)-1*H*-indole-1-carbonyl)-2-(4-methoxyphenyl) cyclopropanecarboxylate (0.070 g, 0.167 mmol), $In(OTf)_3$ (0.028 g, 0.049 mmol) and DCM (3 mL) were combined according to general method A to afford **III-46u** as a brown oil (0.062 g, 88.0%) after 3 h. R_f 0.45 (40% EtOAc/Hex). *Diastereomeric ratio*: (2.0:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.56 – 8.47 (m, 1.45), 7.56 – 7.48 (m, 1.05), 7.44 – 7.28 (m, 3.67), 7.18 – 7.11 (m, 1.06), 7.01 – 6.90 (m, 2.29), 6.88 – 6.78 (m, 3.02), 4.66 (t, *J* = 4.5 Hz, 1), 4.40 (dd, *J* = 9.7, 5.1 Hz, 0.48), 3.90 – 3.81 (m, 1.32), 3.81 – 3.78 (m, 7.54), 3.73 – 3.67 (m, 1.32), 3.64 (s, 1.44), 3.55 (s, 1.42), 3.53 (s, 2.98), 3.52 (s, 0.31), 3.43 (d, *J* = 17.3 Hz, 1.59), 3.32 (d, *J* = 17.7 Hz, 0.85), 3.02 – 2.69 (m, 2.34), 2.58 – 2.38 (m, 1.62). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.8, 170.6, 169.4, 169.1, 165.2, 158.9, 158.8, 136.3, 135.8, 134.6, 134.5, 132.3, 131.9, 130.3, 129.9, 129.2, 128.5, 125.2, 125.2, 124.5, 124.4, 118.4, 118.0, 116.7, 114.2, 114.1, 112.3, 112.0, 55.3, 52.7, 52.6, 52.0, 51.9, 50.1, 47.2, 38.5, 35.4, 34.0, 33.2, 29.7, 29.4. **IR**: 3013.8 (w), 2918.6 (w), 2832.8 (w), 1747.0 (s), 1737.7 (s), 1699.3 (s), 1613.6 (m), 1518.4 (m), 1456.5 (s), 1366.0 (s), 1245.6 (s), 1152.1 (s), 1032.6 (s), 837.3 (m), 731.8 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 421.1525, Obs. 421.1522.



Methyl 6-hydroxy-10-methyl-9-phenylpyrido[1,2-*a*]indole-7-carboxylate (III-47): Methyl 2-bromo-1-(3-methyl-1*H*-indole-1-carbonyl)-2-phenylcyclopropanecarboxylate (0.060 g, 0.145 mmol), $In(OTf)_3$ (0.0245 g, 0.043 mmol) and DCM (3 mL) were combined according to general method A to afford **III-47** as a yellow-green oil (0.013 g, 28.5%) after 4 h. R_f 0.55 (20% EtOAc/Hex). **^{1}H NMR** (300 MHz, CDCl3) δ 12.12 (s, 1H), 8.57 – 8.50 (m, 1H), 7.86 (s, 1H), 7.71 – 7.66 (m, 1H), 7.63 – 7.46 (m, 2H), 7.38 – 7.32 (m, 1H), 7.23 – 7.06 (m, 3H), 6.95 (m, 1H), 3.98 (s, 3H), 2.45 (d, *J* = 1.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.9, 160.7, 138.5, 134.6, 130.3, 128.7, 127.4, 126.5, 125.4, 124.3, 123.7, 123.4, 122.1, 119.4, 119.0, 112.0, 110.5, 105.0, 52.5, 9.7. **IR**: 3600-2800 (br), 2960.3 (m), 2923.7 (m), 2847.4 (m), 1657.1 (s), 1649.7 (s), 1525.7 (m), 1449.7 (s), 1334.3 (m), 1321.1 (m), 1255.4 9s), 1226.3 (s), 1193.8 (w), 1122.6 (m), 1020 (m), 796.6 (s), 740.7 (s), 705.2 (m). **HRMS (ESI)** M/Z+ Calc. 331.1208, Obs. 331.1203.

3.6. REFERENCES

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CHAPTER 4

THE SYNTHESIS OF 1*H*-PYRROLO[1,2-*a*]INDOLES FROM DIASTEREOSELECTIVE INTRAMOLECULAR FRIEDEL-CRAFTS CYCLIZATIONS OF SUBSTITUTED METHYL 2-(1*H*-INDOLE-1-CARBONYL) ACRYLATES[§§]

4.1. INTRODUCTION TO PYRROLO[1,2-*a*]INDOLES

[*a*]-Annelated indoles are heterocyclic ring systems that frequently occur in a wide range of heterocyclic compounds that play important roles in medicinal chemistry and organic synthesis.[1] The pyrrolo[1,2-*a*]-indole ring system, in particular, is a primary target for synthetic chemists due to its structural diversity.[2] The pyrrolo[1,2-*a*]indole heterocyclic skeleton **IV-1** derives the [1,2-*a*] designation through the conceptual fusion of *a* face of an indole **IV-2** with the 1 and 2 positions of a pyrrolidine ring **IV-3.** The positional numbering and ring lettering about the pyrrolo[1,2-*a*]indole core along with above mentioned ring fusion are shown in Figure 4.1.

[§§]This work was performed in collaboration with Marchello A. Cavitt, a fellow graduate student in the France research group.

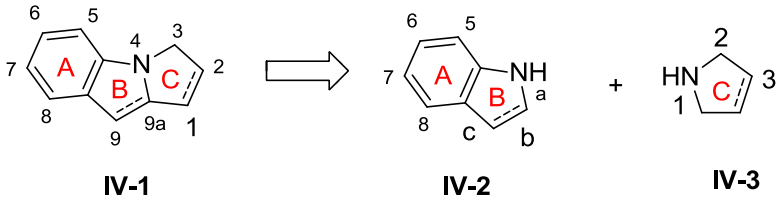


Figure 4.1. Labeling of Pyrrolo[1,2-*a*]indole Core and its Origin from an Indole and a Pyrrolidine Precursor

The pyrrolo[1,2-*a*]indoles are primarily characterized by three isomeric structures (the 9*H*-pyrrolo[1,2-*a*]indoles **IV-4**, the 3*H*-pyrrolo[1,2-*a*]indoles **IV-5**, and the 1*H*-pyrrolo[1,2-*a*]-indoles **IV-6**) or by the two reduced forms **IV-7** and **IV-8** (Figure 4.2).

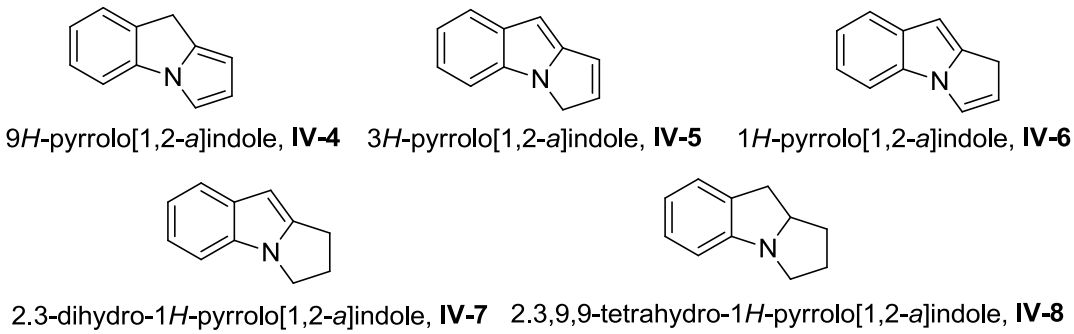


Figure 4.2. Representative Pyrrolo[1,2-*a*]indole Frameworks

Compounds containing pyrrolo[1,2-*a*]-indole core skeleton demonstrate interesting physiological and therapeutic properties.[3] For example, mitomycin C (**IV-9**)[4] exhibits strong anticancer activity; yuremamine (**IV-10**)[5] shows hallucinogenic and psychoactive effects; isatisine A (**IV-11**) possesses antiviral activity;[6] and flinderole C (**IV-12**)[7] acts as a selective antimalarial agent (Figure 4.3).

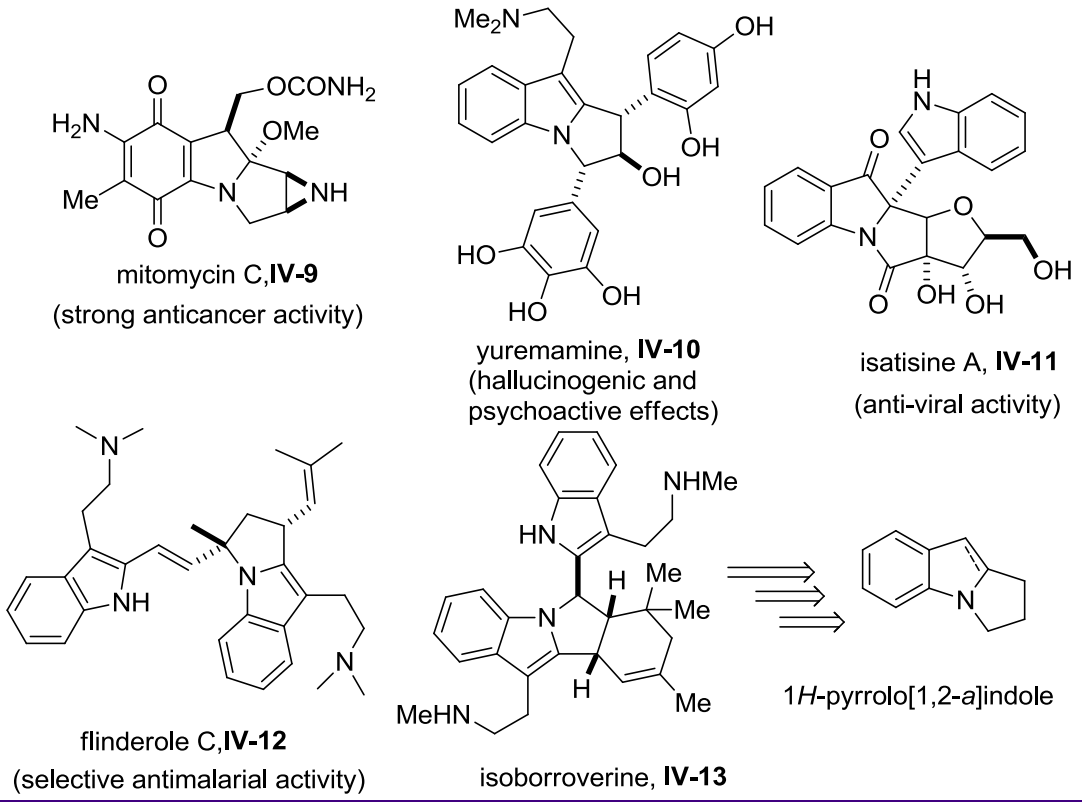


Figure 4.3. Representative Examples of Pyrrolo[1,2-*a*]indole Based Natural Products

4.2. PREVIOUS SYNTHETIC METHODS

Numerous routes have been developed to synthesize and functionalize pyrrolo[1,2-*a*]indoles in recent years,[8,9] underlining the continued importance of this framework to the synthetic community. These routes can be broadly categorized in five main classes **A-E** based upon the order in which the individual ring substructures are introduced. The first three approaches A, B, and C involve synthetic strategies which rely on the construction of A, B, or C rings respectively. The fourth major route D comprises the synthesis of the B and C rings via a transannular ring closure between N4 and C9a. The final class E entails the generation of the B and C rings employing other synthetic strategies. This section will provide a brief overview of some representative approaches

for the construction of pyrrolo[1,2-*a*]indole derivatives with an example given for each synthetic pathway as mentioned in Figure 4.4.

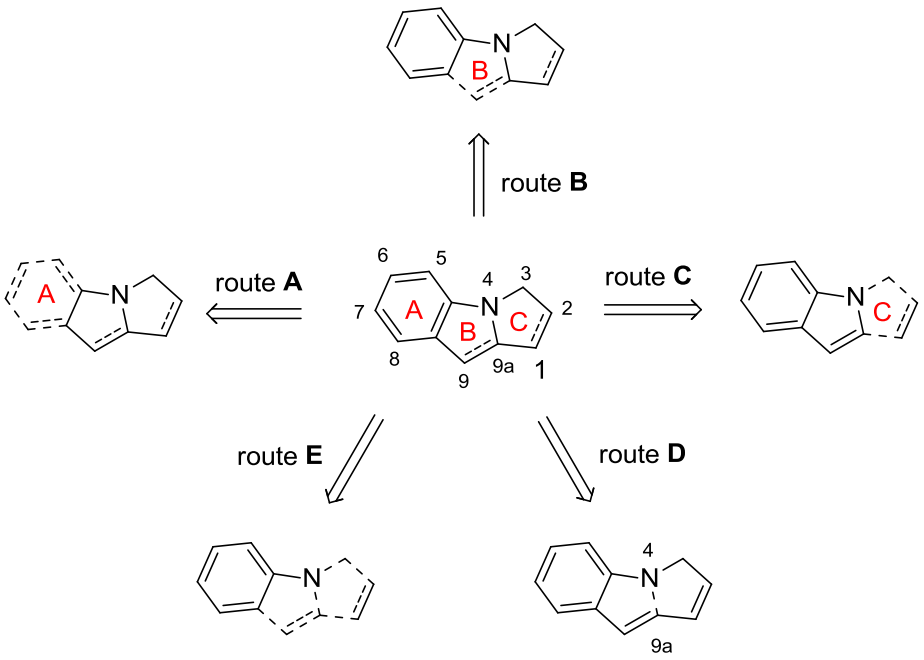


Figure 4.4. Common Synthetic Routes for Pyrrolo[1,2-*a*]indole Derivative Synthesis

4.2.1. PYRROLO[1,2-*a*]INDOLES VIA SYNTHESIS OF THE A RING

The synthesis of pyrrolo[1,2-*a*]indole based derivatives through the formation of A ring is one of the least explored strategies. In 1967, Morlacchi and group reported the formation of pyrrolo[1,2-*a*]benzo[*f*]indole derivatives **IV-17** utilizing a method that generated A ring (Figure 4.5).[10] Upon heating 1-acetamido-1,2-dihydro-pyrrolizine **IV-14** and phthalic anhydride **IV-15** in the presence of large excess of aluminum trichloride, pyrrolo[1,2-*a*]indoles were generated. The reaction proceeds via two sequential Friedel-Crafts reactions. Furthermore, their studies revealed that the when the reaction was carried out at lower temperature and a lower catalyst loading, an intermediate carboxylic acid **IV-16** was observed, which would then undergo second a Friedel-Crafts cyclization

to provide the quinone A ring. An improvement in the yield was observed when the reaction was performed at higher temperature and in one-pot fashion.

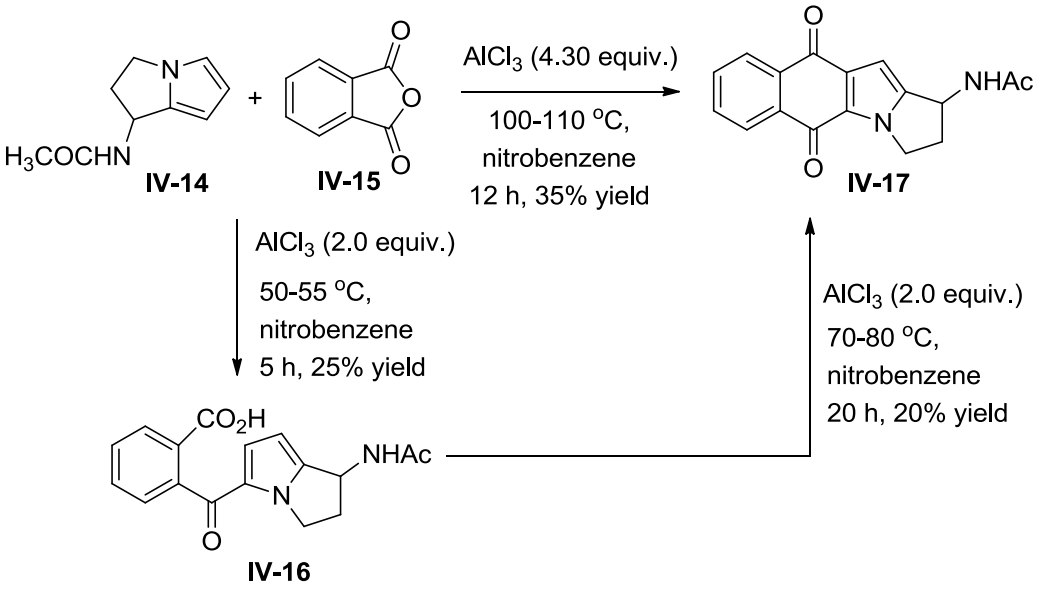


Figure 4.5. Formation of A Ring of the Pyrrolo[1,2-*a*]indoles via Friedel-Crafts Reaction

4.2.2. PYRROLO[1,2-*a*]INDOLES VIA SYNTHESIS OF THE B RING

In an effort to devise an efficient methodology that provides direct access to the privileged *N*-fused indoline scaffold through C(sp^3)-H bond functionalization, the Fillion group developed a novel pyrrolo[1,2-*a*]indole synthesis which falls into the path B classification (Figure 4.6.).[11] They elegantly utilized the ability of *N*-aziridinyl imine **IV-18** to function as a carbene precursor to achieve the desired transformation. The reactions are proposed to proceed through a non-carbonyl-stabilized rhodium carbenoid C-H insertion mechanism to form a five-membered B ring of the pyrrolo[1,2-*a*]indole products. The method furnished *N*-fused indoline products **IV-19** in moderate to high yields. The reactions were optimal at 100 °C in toluene and are usually completed within

3-22 h. The reaction also proceeded in good to high yields with both electron-rich and electron-poor aromatics. The methodology was used in an expedient total synthesis of racemic cryptaustoline.

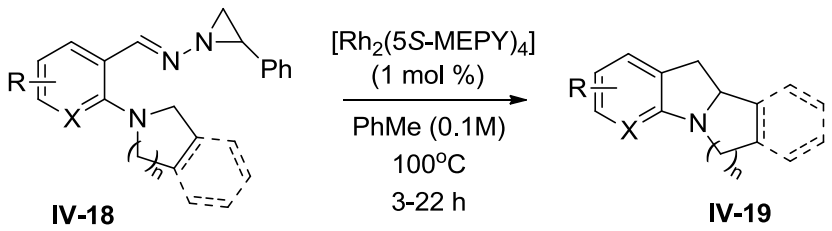


Figure 4.6. Non-Carbonyl-Stabilized Rhodium Carbenoid C-H Insertion of *N*- Aziridinyl Imines to Generate the B Ring.

4.2.3. PYRROLO[1,2-*a*]INDOLES VIA SYNTHESIS OF THE C RING

The generation of pyrrolo[1,2-*a*]indoles via synthesis of the C ring is by far the most common approach. It involves beginning the synthesis with an indole skeleton, and the additional pyrrolo skeleton is built through different transformations. Recently, Wang group reported *N*-heterocyclic carbene catalyzed synthesis of pyrrolo[1,2-*a*]indoles (Figure 4.7.**)**.[9a] The reaction employed 1,1-diactivated FCP with indole-2-carboxaldehydes through NHCs. The reactions are suggested to proceed by NHC-catalyzed domino ring opening/redox amidation/Knoevenagel condensation (a formal hetero-[3+2] cycloaddition) between 1*H*-indole-2-carbaldehyde **IV-21** and readily-available 1,1-diactivated FCP **IV-20** to form the C ring of the pyrrolo[1,2-*a*]indole products. The reactions were optimal at 60-70° C in toluene and are usually completed within 20 h to provide the pyrrolo[1,2-*a*]indole products in moderate to good yields. The Wang group also screened 5-substituted indoles **IV-21**, with both electron-rich and poor

groups and monoactivated FCP, providing products **IV-22** in moderate yields. However, reactions were unsuccessful when tetrasubstituted FCP were tested.

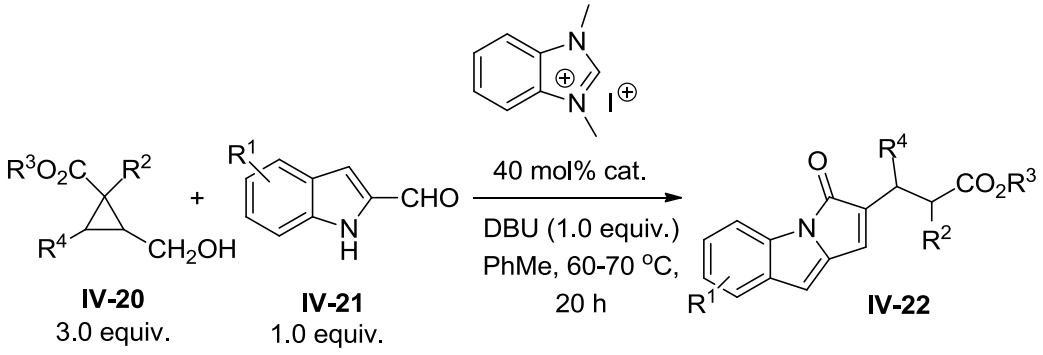


Figure 4.7. *N*-Heterocyclic Carbene Catalyzed Domino Ring-Opening/Redox Amidation/ Knoevenagel Condensation to Generate C Ring

4.2.4. PYRROLO[1,2-*a*]INDOLES VIA SYNTHESIS OF THE D RING

While exploring the utility of the tetrahydro-1,2-oxazine products generated through the reaction of nitrones **IV-23** with 1,1-cyclopropanediesters **IV-24**, the Kerr group developed an efficient route for the synthesis of pyrrolo[1,2-*a*]indoles which relied on a late stage transannular ring closure of amino alcohol **IV-26** (Figure 4.8).[12] Initial studies focused on N-O bond cleavage of FR900482 skeletal congener **IV-25** using an acid zinc reduction and a hydrogenolysis route. However, reactions under these conditions either failed to provide higher product conversions or desired products. Fortunately, SmI_2-mediated N-O bond reduction of the monoester occurred to afford amino alcohol **IV-26**. The resulting alcohol was subjected to acid-catalyzed transannular ring closure to form the desired product **IV-27**. Therefore, synthesis of desired pyrrolo[1,2-*a*]indole skeletons involves a five-step sequence (cycloaddition, Heck cyclization, Krapcho decarboxylation, SmI_2-mediated N-O bond reduction, and acid-catalyzed transannular ring closure).

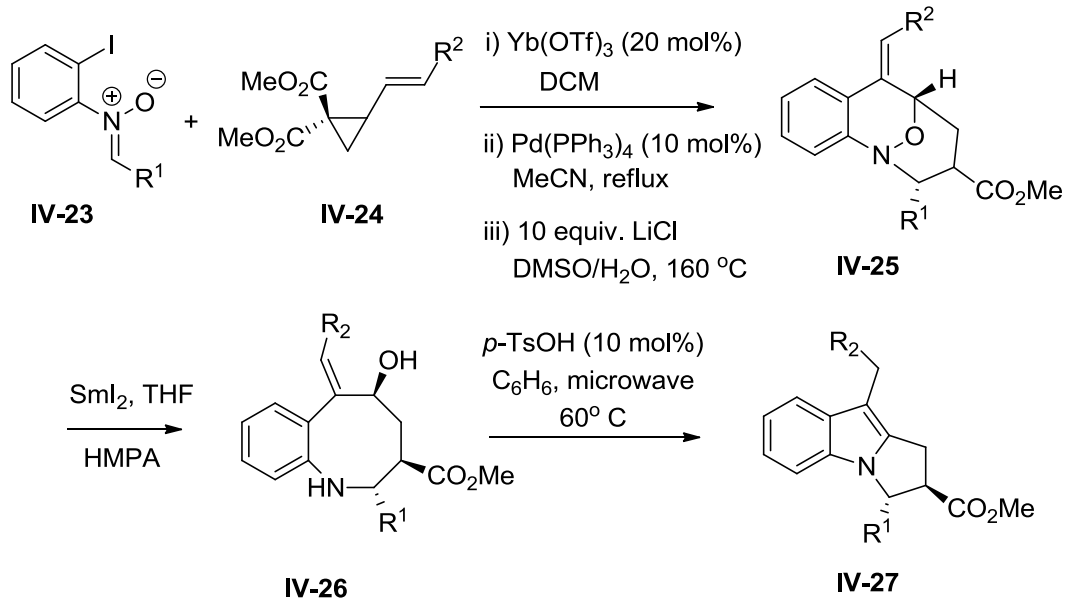


Figure 4.8. Acid Catalyzed Transannular Ring Closure Approach for D Ring Synthesis

4.2.5. PYRROLO[1,2-*a*]INDOLES VIA SYNTHESIS OF THE E RING

The final class of reaction towards the synthesis of pyrrolo[1,2-*a*]indoles involves the formation of the B and C rings. Recently, the Feldman group reported allenyl azide cycloaddition chemistry to generate cyclopentannelated indoles (Figure 4.9).[13] The reaction employed a 2-(allenyl)phenyl azide as a cyclization substrate. Upon subjecting this azide to toluene solution at reflux conditions, it furnished the expected product C(2)-C(3) annelated indole **IV-29** accompanied by N-C(2) annelated indole product **IV-30**. This reaction proceeds through an indolidene intermediate. The reaction tolerates silyl ether and steric bulk at the R^2 position. Interestingly, these studies revealed that upon addition of steric bulk at the R^2 positions, ratios of C(2)-C(3) to N-(C2) products can be modulated. The substituents at the internal R position did not alter product ratios.

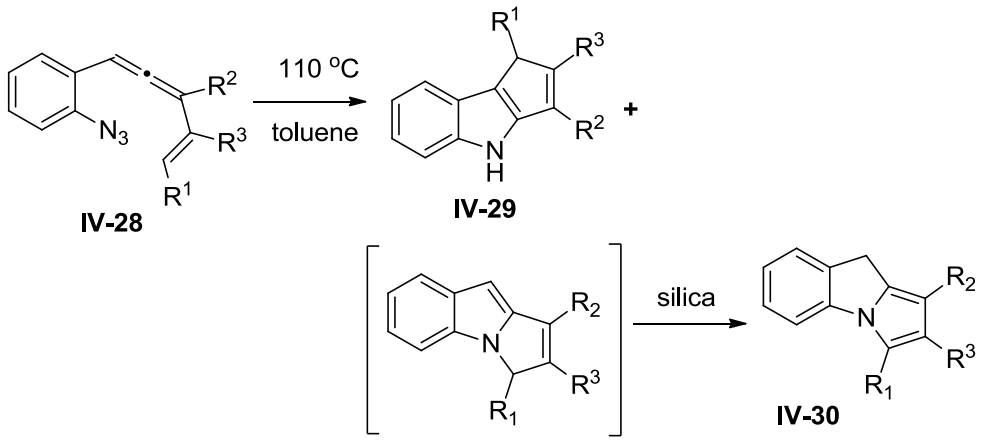


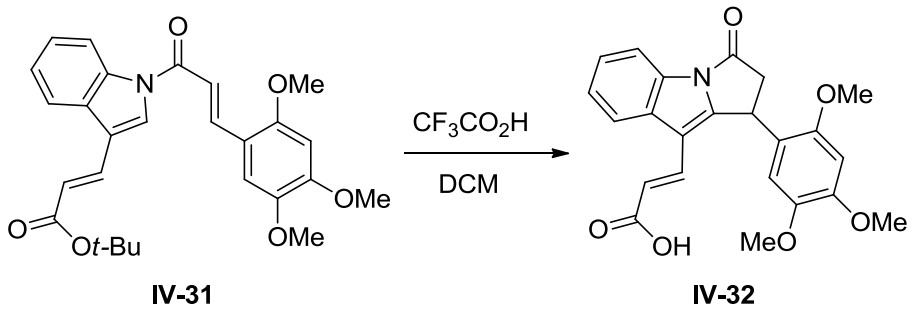
Figure 4.9. Allenyl Azide Cycloaddition Approach to Generate E Ring

4.3. THE DEVELOPMENT OF INDIUM(III)-CATALYZED DIASTEREOSELECTIVE INTRAMOLECULAR FRIEDEL-CRAFTS CYCLIZATION OF METHYL 2-(1*H*-INDOLE-1-CARBONYL) ACRYLATES

The Michael-type F-C reaction of indoles with α,β-unsaturated carbonyl compounds is a powerful strategy in the total synthesis of complex products.[14] While intermolecular examples of these reactions are prevalent in the literature,[15] the lesser studied intramolecular variants offer tremendous utility for the synthesis of complex indole-containing polycycles.[16] Following our success with the development of an efficient synthesis of hydropyrido-[1,2-*a*]indole-6(7*H*)-ones via an In(III)-catalyzed tandem cyclopropane ring-opening/intramolecular F-C alkylation sequence,[17] we reasoned that an intramolecular F-C reaction should occur if the corresponding methyl 2-(1*H*-indole-1-carbonyl)acrylates **IV-35** were employed as the cyclization precursors.

Adding credence to this hypothesis, Hadjipavlou-Litina and Papaioannou recently reported the formation of a 1*H*-pyrrolo[1,2-*a*]indole-3(2*H*)-one.[18] While performing

TFA-mediated deprotection of an *N*-cinnamoyl indole ester derivative **IV-31** to its corresponding acid, the rearranged acid **IV-32** was isolated in 84% yield. The reaction was proposed to go through an acid-mediated Michael-type nucleophilic attack mechanism for the formation of this unexpected product (Figure 4.10). This reaction only occurred when the aryl portion of the cinnamate had electron-donating *ortho*- and *para*-methoxy substituents. When no methoxy group was present or if the aryl ring had only one methoxy group in the *ortho*- or *para*-position, rearrangement was not observed.



IV-31 **IV-32**

Figure 4.10. Hadjipavlou-Litina's Example of TFA-Catalyzed Michael-Type Nucleophilic Reaction

4.3.1. PROOF OF PRINCIPLE

In hopes of circumventing this limitation and given that alkylidene malonates have been shown to offer enhanced reactivity as Michael acceptors in comparison to simple *α*, *β*-unsaturated alkenes,[19] *N*-acylated indoles **IV-35a** were synthesized as shown in Figure 4.11. Treatment of 3-methyl-1*H*-indole **IV-33a** with methyl malonyl chloride (MMC) afforded the β-amide ester **IV-34a**, and Knoevenagel condensation with a *p*-anisaldehyde furnished the desired acrylates **IV-35a** in high yields.

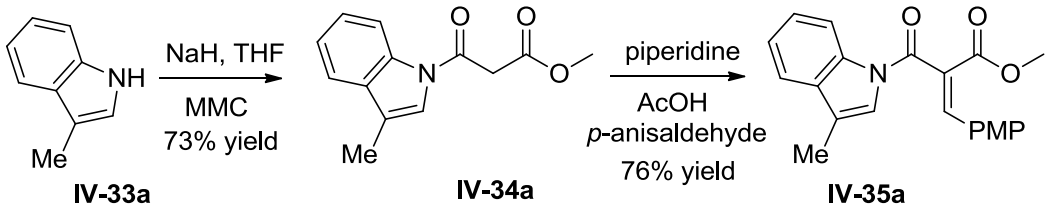
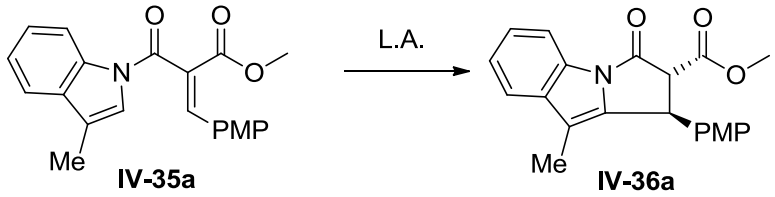


Figure 4.11. Synthesis of Substituted Methyl 2-(1*H*-indole-1-carbonyl)acrylate

With a model substrate in our hand, we set out to test the feasibility of our hypothesis by subjecting it to the reaction conditions (30 mol% $In(OTf)_3$, DCM, rt) employed in our recent synthesis of hydropyrido[1,2-*a*]indoles. To our surprise, the utilization of this reaction conditions at room temperature or even at higher temperature (40 ^oC) did not lead to the formation of any products (Table 4.1, entry 1-2). Interestingly, a quantitative conversion to the desired product (>98% yield) of **IV-36a** was realized when the reaction was heated at 110 °C for 0.5 h using 30 mol% $In(OTf)_3$ in toluene and column chromatography (Table 4.1, entry 3). Using the model substrate **IV-35a,** a series of experiments were performed with variation of reaction parameters such as catalyst, % loading of catalyst, solvent, temperature, etc., in hopes of optimizing the formation of pyrrolo[1,2-*a*]indole product **IV-36a**. Selected results are summarized in Table 4.1. In order to find the effect of temperature, toluene solvent was replaced by 1,2-dichloroethane and the reaction was performed at 80 °C. Gratifyingly, the reaction still showed quantitative conversion to the product (Table 4.1, entry 4). Next, the substoichiometric amounts of various metal catalysts, primarily focusing on readily available triflate salts, were tested. Of the catalyst screened, Sc^{3+}, Al^{3+}, Cu^{2+}, and Yb^{3+} showed complete consumption of starting material. While it was possible to move forward with any of the above catalyst system, $In(OTf)_3$ was chosen as the catalyst

system given the slightly shorter reaction times. Finally, the effect of varying catalyst amounts was examined. Using 5 mol % $In(OTf)_3$ led to a increased reaction time. Therefore, heating the reactants in 1,2-dichloromethane at reflux in the presence of 10 mol % $In(OTf)_3$ as the catalyst is chosen as the optimized reaction condition.

Table 4.1. Optimization of the Reaction Conditions



IV-35a **IV-36a**

entry	% mol loading	conditions	time (h)	conversion[a]
1	30% $In(OTf)_3$	DCM, 25°C	48[b]	---[c]
2	30% $In(OTf)_3$	DCM, 50°C	48[b]	---[c]
3	30% $In(OTf)_3$	toluene, 110°C	0.5	100%
4	30% $In(OTf)_3$	1,2-DCE, 80°C	.75	100%
5	10% $In(OTf)_3$	1,2-DCE, 80°C	1	100%
6	10% $Sc(OTf)_3$	1,2-DCE, 80°C	1.5	100%
7	10% $Al(OTf)_3$	1,2-DCE, 80°C	1.5	100%
8	10% $Cu(OTf)_2$	1,2-DCE, 80°C	9	100%
9	10% $Yb(OTf)_3$	1,2-DCE, 80°C	10	100%
10	10% $Zn(OTf)_2$	1,2-DCE, 80°C	48[b]	45%
11	5% $In(OTf)_3$	1,2-DCE, 80°C	2	100%

[a] Conversion determined by crude ^1H NMR. [b] Reaction stopped after indicated time. [c] No reaction observed.

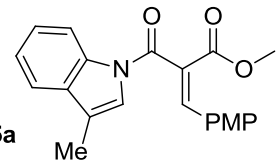
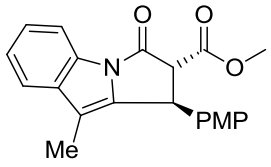
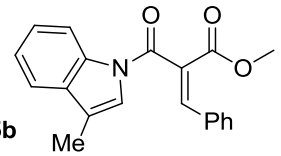
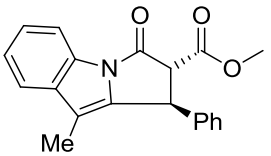
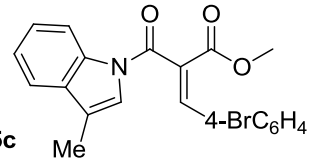
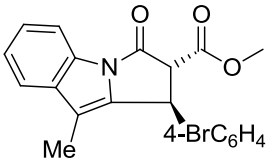
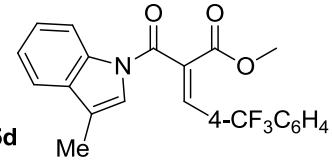
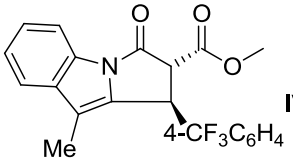
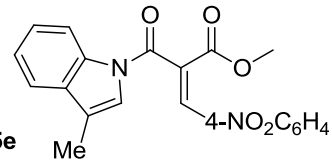
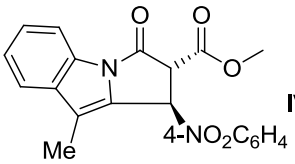
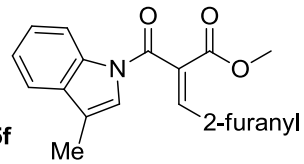
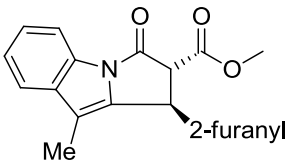
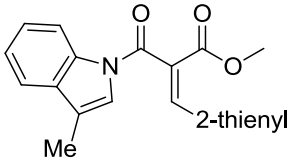
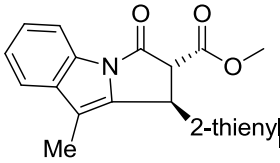
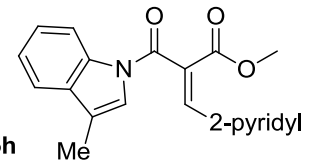
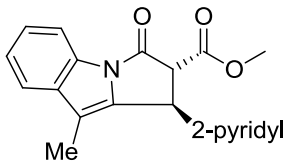
4.3.2. RESULTS AND DISCUSSION

Having established the optimized reaction conditions (Table 4.1, entry 5), next extension of the reaction scope to a variety of aryl substituted acrylates was sought (Table 4.2). The sequence proved to be quite general, providing rapid access to a range of diversely functionalized 1*H*-pyrrolo[1,2-*a*]indole products **IV-36**. The model substrate **IV-35a** furnished 1*H*-pyrrolo[1,2-*a*]indole product **IV-36a** in 95% yield with a 15:1 *trans/cis dr* (Table 4.2, entry 1). To determine the electronic effect of the aryl substituent on the product formation, substrates with the phenyl group **IV-35b** and the electron-withdrawing 4-bromophenyl (**IV-35c)**, 4-trifluoromethylphenyl (**IV-35d)**, and the 4-nitrophenyl (**IV-35e)** groups were prepared using our three step sequence. The phenyl derivative readily cyclized to afford **IV-36b** in 97% yield with a 16:1 *dr* (Table 4.2, entry 2). The reaction was found to be equally effective with the electron deficient arenes to furnish products in high yields (Table 4.2, entries 3-5). Therefore, no discernible effect on the reaction outcome was observed due the variation of electronic properties of the functional groups attached with the aryl acrylates. Next, electron-rich heteroaromatic substituted acrylates were considered. The 2-substituted furanyl derivative **IV-35f** and 2-thienyl derivative **IV-35g**, proved to be suitable substrates, providing 1*H*-pyrrolo[1,2-*a*]indole products **IV-36f** and **IV-36g** in 97% and 98% yield, respectively, with high *dr* (Table 4.2, entries 6 and 7). In contrast, the 2-pyridyl substrate **IV-35h** did not undergo any appreciable cyclization (Table 4.2, entry 8). This lack of reactivity may be attributed to inductive effects, given that the 2-pyridyl group prefers to serve as an electron acceptor. Moreover, the nitrogen of the pyridine could serve to deactivate the Indium catalyst by forming a stable complex.

The cyclization protocol is also amenable to substituent changes about the 3-position of the indole moiety (Table 4.3). For example, when the phthalimide-protected tryptamine derivative **IV-35i** was subjected to the reaction conditions, 1*H*-pyrrolo[1,2-*a*]-indole product **IV-36i** was generated in 96% yield with 14:1 *dr* (Table 4.3, entry 1). Moreover, **IV-36i** can then be readily deprotected to provide the free amine, which is important for several natural product targets, such as the flinderoles **IV-12**. The 3-(2-bromoethyl)-1*H*-indole derivative **IV-35j** also provided its cyclization product **IV-36j** in 69% yield with a 25:1 *dr* (Table 4.3, entry 2). The bromide on this molecular scaffold provides an excellent handle for further functionalization. The methyl acetate substituted indole derivative **IV-35k** generated its cyclized product **IV-36k** in 93% yield with 13:1 *dr* (Table 4.3, entry 3). Finally, when substrate **IV-35l** (derived from indole) was employed, the cyclization readily occurred to afford **IV-36l** in 98% yield and 10:1 *dr* (Table 4.3, entry 4).

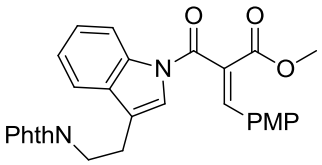
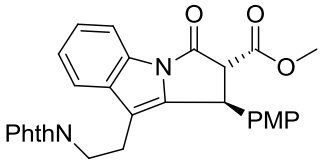
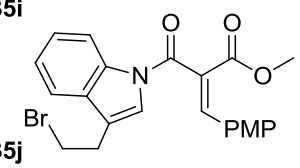
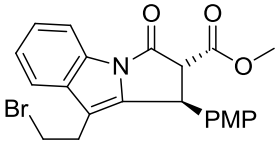
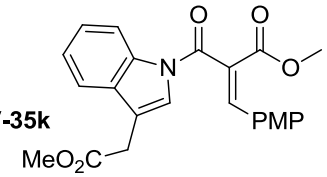
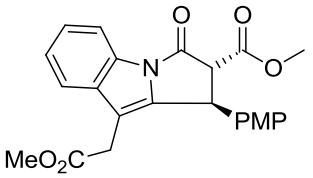
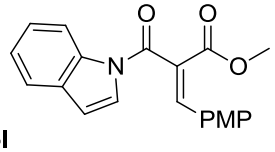
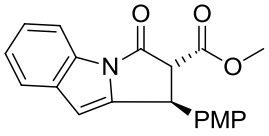
While pleased with the performance of the aromatic substrates, nonaromatic substituents on the acrylates were considered for further expansion of the substrate scope (Table 4.4). In particular, we were interested in systems derived from alkyl aldehydes and cinnamaldehyde. The ethyl substituted acrylate **IV-35m** was the first nonaromatic substrate synthesized. Unfortunately, no reaction was observed by subjecting **IV-35m** to the optimized conditions. After careful screening of various conditions, it was found that the cyclization of **IV-35m** could be achieved at a slightly higher catalyst loading (15%) in toluene heated at reflux. Under these new conditions, the cyclized product **IV-36m** was furnished in 89% yield as the *trans* isomer (Table 4.4, entry 1).

Table 4.2. Results of Friedel-Crafts Alkylation with Aromatic Acrylates[a]

entry	substrate	product	% yield[b]	*dr*[c]
1	 **IV-35a**	 **IV-36a**	95	15:1
2	 **IV-35b**	 **IV-36b**	97	16:1
3	 **IV-35c**	 **IV-36c**	93	16:1
4	 **IV-35d**	 **IV-36d**	92	20:1
5	 **IV-35e**	 **IV-36e**	84	19:1
6	 **IV-35f**	 **IV-36f**	97	18:1
7	 **IV-35g**	 **IV-36g**	98	24:1
8	 **IV-35h**	 **IV-36h**	no reaction	

[a] Reactions run with substrate (1 equiv.) and $In(OTf)_3$ (10 mol %) in 1,2-dichloroethane at reflux. [b] Isolated yields after column chromatography. [c] Diastereoselectivities determined from ^1H NMR of the crude reaction mixture and represent trans/cis diastereomeric ratio.

Table 4.3. Effect of Indole Substituents on Friedel-Crafts Alkylation Reaction[a]

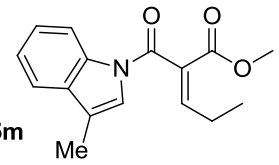
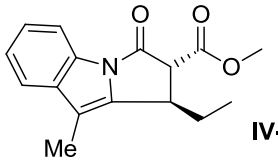
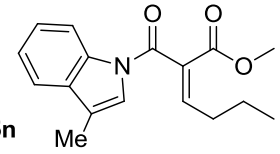
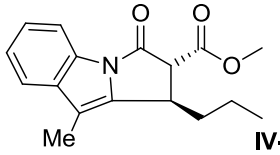
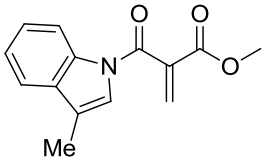
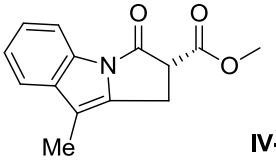
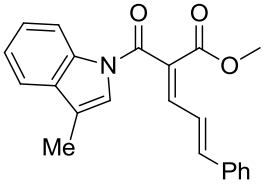
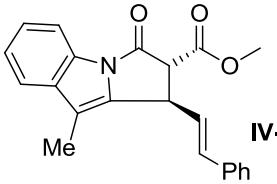
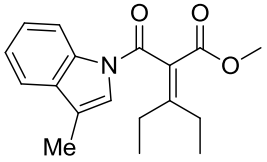
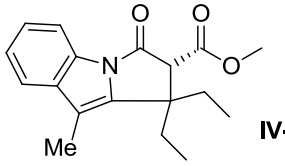
entry	substrate	product	% yield[b]	*dr*[c]
1	 **IV-35i**	 **IV-36i**	96	14:1
2	 **IV-35j**	 **IV-36j**	69	25:1
3	 **IV-35k**	 **IV-36k**	93	13:1
4	 **IV-35l**	 **IV-36l**	98	10:1

[a] Reactions run with substrate (1 equiv.) and $In(OTf)_3$ (10 mol %) in 1,2-dichloroethane at reflux. [b] Isolated yields after column chromatography. [c] Diastereoselectivities determined from ^1H NMR of the crude reaction mixture and represent *trans/cis* diastereomeric ratio.

Similar reactivity was observed for the propyl substituted derivative **IV-35n** (Table 4.4, entry 2). The parent compound, methyl 2-(1*H*-indole-1-carbonyl)acrylate **IV-35o** (derived from formaldehyde), gave the 1*H*-pyrrolo[1,2-*a*]indole product **IV-36o** in 47% yield (Table 4.4, entry 3). Cinnamate **IV-35p** (from cinnamaldehyde) afforded its product **IV-36p** in 71% yield with 8:1 *dr* (Table 4.4, entry 4). We were delighted to find that the 2,2-disubstituted acrylate **IV-35q** (derived from 3-pentanone) cyclized to generate product **IV-36q**, containing a quaternary carbon, in 98% yield (Table 4.4, entry 5). This reaction proceeds quite well even with a substrates derived from ketones and

offers a powerful method to generate a functionalized quaternary carbon, especially, if an unsymmetric ketone is used.

Table 4.4. Scope of Friedel-Crafts Alkylation Reaction with Nonaromatic Acrylates[a]

entry	substrate	product	% yield[b]	*dr*[c]
1	 **IV-35m**	 **IV-36m**	89	--[d]
2	 **IV-35n**	 **IV-36n**	84	--[d]
3	 **IV-35o**	 **IV-36o**	47	--
4	 **IV-35p**	 **IV-36p**	71	8:1
5	 **IV-35q**	 **IV-36q**	98	--

[a] Reactions run with substrate (1 equiv.) and $In(OTf)_3$ (15 mol %) in toluene at reflux. [b] Isolated yields after column chromatography. [c] Diastereoselectivities determined from ^1H NMR of the crude reaction mixture and represent trans/cis diastereomeric ratio. [d] Only one diastereomer observable by crude NMR.

An interesting result was obtained when acrylate **IV-35r** (derived from isobutyraldehyde) was subjected to the modified conditions. While the reaction formed the anticipated *trans*-1*H*-pyrrolo[1,2-*a*]indole product **IV-36r** in 86% yield, a small amount of the hydropyrido[1,2-*a*]-indole product **IV-37** was also observed. The formation of this minor product could be attributed to a mechanistic pathway delineated in Figure 4.12. This product seemingly arises from a putative carbocationic intermediate **A** that undergoes a 1,2-hydride shift to generate carbocation **B**, an intermediate observed in our tandem cyclopropane ring-opening/intramolecular FC cyclization.[17] Intermediate **B** then undergoes an intramolecular FC reaction to generate the six-membered ring in **IV-37**. Frontier recently noted this type of transformation for alkenyl 2-furyl and alkenyl 2-benzofuryl ketones in the presence of a highly Lewis acidic Ir^{3+} catalyst.[20] Both examples highlight the existence of two possible pathways that depend on the aromatic character of the heteroaryl moiety as well as the Lewis acid catalyst.

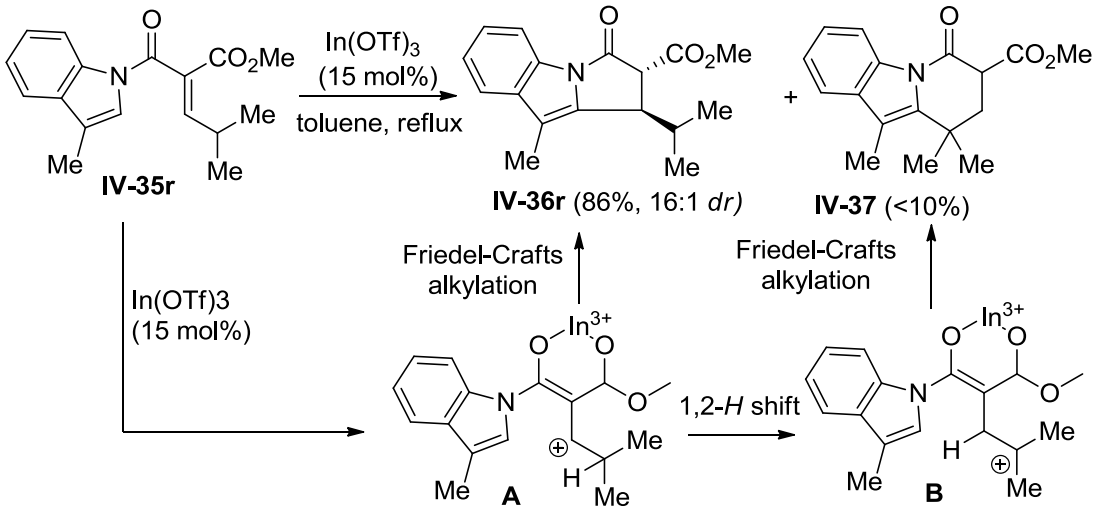
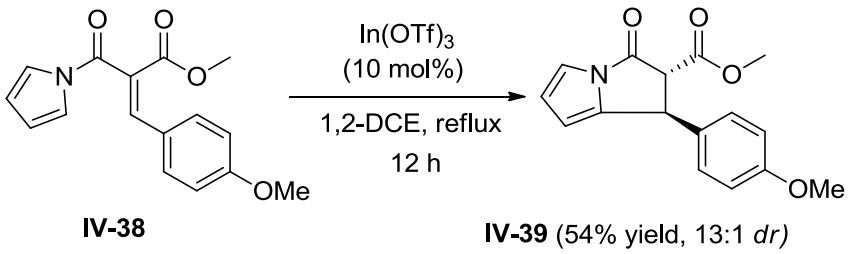


Figure 4.12. Proposed Pathway for the Observed Hydropyrido[1,2-*a*]indole Product

Finally, to expand the scope of this synthetic approach, we set out to perform a preliminary test reaction on a different heteroaromatic. Given that the cyclization readily occurs with indoles, we anticipated that pyrroles would behave similarly under the reaction conditions to form 1*H*-pyrrolizin-3(2*H*)-ones. Pyrrolizine derivatives, many of which are naturally occurring, have attracted considerable attention from both synthetic and medicinal chemists for their interesting biological activities and therapeutic potential.[21] To our satisfaction, when *N*-acyl pyrrole **IV-38** was treated with $In(OTf)_3$ in 1,2-dichloroethane at reflux, the expected pyrrolizine product **IV-39** was obtained in 54% yield (unoptimized) with 13:1 *dr* (Figure 4.13.).



IV-38 **IV-39** (54% yield, 13:1 *dr)*

Figure 4.13. Test Reaction using Pyrrole as an Effective Substrate

4.4. CONCLUSIONS AND FUTURE WORK

In conclusion, a facile and efficient method for the synthesis of functionalized 1*H*-pyrrolo-[1,2-*a*]indole-3(2*H*)-ones has been through a Lewis acid-catalyzed diastereoselective intramolecular Friedel-Crafts reaction of substituted methyl 2-(1*H*-indole-1-carbonyl)acrylates. The method is fast, operationally simple, and versatile enough to access a variety of pyrrolo[1,2-*a*]indoles. The reactions proceeded efficiently with a wide variety of substrates and afforded the corresponding products in high yields (up to 98%) with high diastereoselectivities (up to >25:1 *dr*) from simple, readily available substances such as indoles and aldehydes.

In future, this methodology may find application in the total synthesis of the yuremamine and Flinderole C natural products. Efforts to employ chiral catalyst complexes to promote enantioselectivity as well as further examination of the cationic rearrangement pathway are currently underway.

4.5. EXPERIMENTAL

4.5.1. General Methods

All reactions were carried out in pre-dried glassware from the oven and any additional moisture was removed by flame-drying the reaction vessel. Each reaction proceeded under a nitrogen atmosphere with anhydrous solvents, unless stated otherwise. Tetrahydrofuran and diethyl ether were distilled from a sodium/benzophenone ketyl under nitrogen and stored in a Schlenk flask. Benzene, toluene, 1,2-dichloroethane and dichloromethane were purified by distillation from calcium hydride. Acetonitrile was dried by fractional distillation over CaH_2. All other reagents were purchased from Acros, Sigma-Aldrich, Fluka, VWR, Merck, Alfa Aesar, TCI and Strem (for metal catalysts) and used without further purification. All methyl 3-(1*H*-indol-1-yl)-3-oxopropanoates **IV-34** were synthesized as previously reported**.**[17]

Chromatographic purification was performed as flash chromatography with Dynamic Adsorbents silica gel (32-65μm) and solvents indicated as eluent with 0.1-0.5 bar pressure. For quantitative flash chromatography, technical grades solvents were utilized. Analytical thin-layer chromatography (TLC) was performed on EMD silica gel 60 F_{254} TLC glass plates. Visualization was accomplished with UV light, aqueous basic potassium permanganate ($KMnO_4$) solution, iodine, aqueous acidic dinitrophenylhydrazine (DNP) solution, aqueous acidic *p*-anisaldehyde (PAA) solution, and an ethanol solution of phosphomolybdic acid (PMA) followed by heating. Each yield refers to an isolated, analytically-pure material.

Infrared (IR) spectra were obtained using a Nicolet 4700 FTIR with an ATR attachment from SmartOrbit Thermoelectronic Corp. The IR bands are characterized as

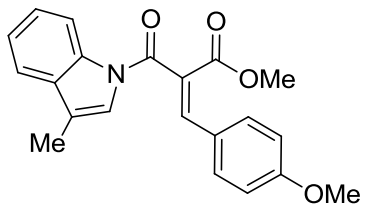
weak (w), medium (m), and strong (s). Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Varian Mercury Vx 300 MHz spectrometer, Varian Mercury Vx 400 MHz spectrometer or Bruker 400 MHz spectrometer with solvent resonances as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, t = triplet, m = multiplet), coupling constants (Hz), and integration. Mass spectra were obtained using a VG-70SE instrument.

4.5.2. Preparation of Acrylate Products IV-35a-r, IV-38

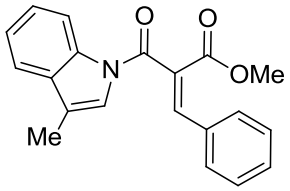
General Method A:[22] The β-ester-amide (1.0 equiv.), aldehyde (1.3 equiv.), glacial acetic acid (0.5 equiv.), and piperidine (0.1 equiv.) were heated to a reflux in benzene using a Dean-Stark trap for 12 h. After cooling the reaction mixture to room temperature, water was added to the reaction vessel, and the organic layer was collected. Subsequently, the aqueous phase was extracted with EtOAc three times. The combined organic layers were washed with 1 M HCl and saturated sodium bicarbonate. The combined organic layers were dried with Na_2SO_4, filtered, concentrated, and purified by silica gel column chromatography (gradient EtOAc/Hex).

General Method B:[23] A round bottom flask was charged with the β-ester-amide (1.0 equiv.) and THF (25 mL). After cooling the solution to 0 ˚C, titanium(IV) chloride tetrahydrofuran complex (2.0 equiv.) and CCl_4 (2.0 equiv.) were added to the reaction vessel. After 1h at 0 ˚C, the aldehyde (1.0 equiv.) was added slowly, and the reaction was stirred for an hour. Then, pyridine (4.0 equiv.) was added to the solution drop-wise. The

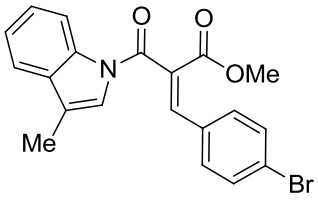
reaction mixture was warmed to room temperature and allowed to stir for 14 h. The reaction was quenched with water and the organic layer was collected. The aqueous layer was extracted with ether, and the combined organic layers were washed with saturated $NaHCO_3$ and brine. The organic layer was dried with $MgSO_4$, filtered, concentrated, and purified by silica gel column chromatography (gradient EtOAc/Hex).



(*Z*)-Methyl 3-(4-methoxyphenyl)-2-(3-methyl-1*H*-indole-1-carbonyl)acrylate (IV-35a): Methyl 3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.800 g, 3.46 mmol), 4-methoxybenzaldehyde (0.53 mL, 4.32 mmol), glacial acetic acid (0.0956 g, 1.59 mmol), piperidine (0.0295 g, 0.346 mmol) and benzene (15 mL) were mixed according to general method A to afford **IV-35a** as a white solid (0.920 g, 76%) after 18 h. R_f 0.30 (20% EtOAc/Hex). [**m.p.** 138-140 °C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.69 (d, *J* = 8.1 Hz, 1H), 7.94 (s, 1H), 7.53 – 7.32 (m, 5H), 7.01 (s, 1H), 6.79 – 6.72 (m, 2H), 3.80 (s, 3H), 3.70 (s, 3H), 2.18 (d, *J* = 0.6 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.2, 164.9, 161.7, 142.9, 135.3, 132.1, 131.9, 125.2, 124.6, 124.1, 123.3, 122.4, 119.1, 118.8, 116.7, 114.5, 55.1, 52.6, 9.5. **IR**: 3070.1 (w), 3007.0 (w), 2930.6 (w), 2824.4 (w), 1715.1 (m), 1678.1 (s), 1598.3 (s), 1511.9 (m), 1448.1 (m), 1395.8 (m), 1341.2 (m), 1254.3 (s), 1170.5 (s), 1047.5 (s), 874.9 (m), 732.2 (s), 698.5 (m), 536.2 (m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 349.1314, Obs. 349.1314.

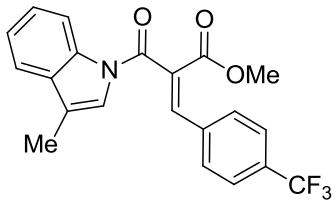


(*Z*)-Methyl 2-(3-methyl-1*H*-indole-1-carbonyl)-3-phenylacrylate (IV-35b): Methyl 3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.350 g, 1.51 mmol), benzaldehyde (0.19 mL, 1.89 mmol), glacial acetic acid (0.0418 g, 0.696 mmol), piperidine (0.0129 g, 0.151 mmol) and benzene (15 mL) were combined according to general method A to yield **IV-35b** as a pale yellow solid (0.260 g, 52%) after 12 h. R_f 0.50 (20% EtOAc/Hex). [**m.p.** 112-114 °C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.59 (d, *J* = 8.1 Hz, 1H), 7.92 (s, 1H), 7.47 – 7.17 (m, 8H), 6.90 (s, 1H), 3.76 (s, 3H), 2.12 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 164.8 (2), 143.3, 135.5, 132.2, 132.1, 131.1, 129.9, 129.1, 126.2, 125.4, 124.2, 122.3, 119.5, 118.9, 116.9, 52.9, 9.7. **IR**: 3056.8 (w), 3026.9 (w), 2957.2 (w), 2914.0 (w), 2850.9 (w), 1723.0 (s), 1711.5 (s), 1687.9 (s), 1678.3 (s), 1615.5 (m), 1449.5 (m), 1396.5 (m), 1341.9 (m), 1256.7 (s), 1212.4 (s), 1198.5 (s), 1046.7 (m), 881.6 (m), 731.6 (s), 687.4 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 319.1208, Obs. 319.1217.



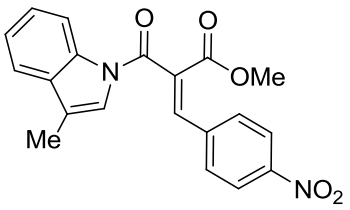
(*Z*)-Methyl 3-(4-bromophenyl)-2-(3-methyl-1*H*-indole-1-carbonyl)acrylate (IV-35c): Methyl 3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.500 g, 2.16 mmol), 4-bromobenzaldehyde (0.500 g, 2.70 mmol), glacial acetic acid (0.0520 g, 0.867 mmol), piperidine (0.184 g, 0.216 mmol) and benzene (30 mL) were mixed according to general

method A to afford **IV-35c** as a colorless oil (0.418 g, 49%) after 12 h. R_f 0.30-0.35 (20% EtOAc/Hex). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.54 (d, *J* = 8.1 Hz, 1H), 7.82 (s, 1H), 7.47 – 7.17 (m, 7H), 6.84 (s, 1H), 3.74 (s, 3H), 2.10 (d, *J* = 1.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 164.5, 164.4, 141.8, 135.4, 132.4, 132.1, 131.2, 131.0, 126.9, 125.7, 125.5, 124.4, 122.0, 119.8, 119.0, 116.8, 53.0, 9.7. **IR**: 3030.2 (w), 2940.6 (w), 2914.0 (w), 2841.0 (w), 1731.7 (m), 1698.5 (s), 1672.0 (m), 1619.7 (s), 1585.6 (m), 1439.5 (m), 1392.7 (m), 1250.8 (s), 1212.1 (m), 1178.7 (m), 1073.0 (m), 1006.8 (m), 964.6 (m), 737.1 (s), 700.3 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 397.0314, Obs. 397.0303.

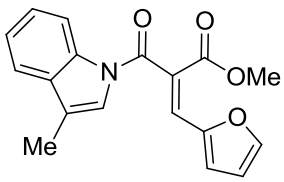


(***Z*)-Methyl2-(3-methyl-1*H*-indole-1-carbonyl)-3-(4-(trifluoromethyl)phenyl)acrylate (IV-35d):** Methyl 3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.500 g, 2.16 mmol), 4-(trifluoromethyl)benzaldehyde (0.470 g, 2.70 mmol), glacial acetic acid (0.0520 g, 0.867 mmol), piperidine (0.184 g, 0.216 mmol) and benzene (30 mL) were combined according to general method A to afford **IV-35d** as a white solid (0.523 g, 62%) after 12 h. R_f 0.30-0.35 (20% EtOAc/Hex). [**m.p.** 78-80 °C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.62 (d, *J* = 8.1 Hz, 1H), 7.98 (s, 1H), 7.63 – 7.33 (m, 7H), 6.91 (s, 1H), 3.84 (s, 3H), 2.18 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 164.3, 164.0, 141.3, 135.6, 135.4, 132.5, 132.1, 129.9, 128.7, 126.05, 126.0, 125.6, 125.3, 124.5, 121.8, 120.1, 119.0, 116.9, 53.1, 9.7. **IR**: 3096.7 (w), 3066.8 (w), 2920.7 (w), 2854.2 (w), 1725.9 (s), 1688.2 (s), 1678.6 (s), 1622.1 (w), 1450.6 (s), 1396.8 (s), 1322.3 9s), 1257.5 (s), 1213.2 (m), 1167.8 (m), 1118.6 (s), 1068.1 (s),

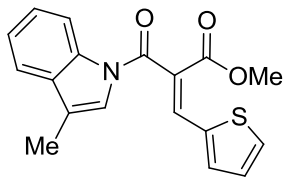
1014.4 (m), 874.9 (w), 835.1 (w), 748.0 (s), 682.3 (w) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 387.1082, Obs. 387.1084.



(*Z*)-Methyl 2-(3-methyl-1*H*-indole-1-carbonyl)-3-(4-nitrophenyl)acrylate (IV-35e): Methyl 3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.350 g, 1.51 mmol), 4-nitrobenzaldehyde (0.286 g, 1.89 mmol), glacial acetic acid (0.0418 g, 0.696 mmol), piperidine (0.0128 g, 0.151 mmol) and benzene (15 mL) were mixed according to general method A to afford **IV-35e** as a yellow solid (0.246 g, 43%) after 12 h. R_f 0.30 (20% EtOAc/Hex). [**m.p.** 147-149 °C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.58 (d, *J* = 7.4 Hz, 1H), 8.12 (d, *J* = 8.3 Hz, 2H), 7.99 (s, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.53 – 7.34 (m, 3H), 6.86 (s, 1H), 3.85 (s, 3H), 2.17 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 164.0, 163.5, 148.5, 141.9, 140.1, 138.3, 135.4, 132.0, 130.3, 130.1, 128.6, 125.8, 124.6, 124.2, 121.5, 120.4, 119.1, 116.8, 53.3, 9.7. **IR**: 3100.0 (m), 3060.2 (m), 2957.2 (m), 2914.0 (m), 2834.3 (m), 1724.6 (s), 1687.1 (s), 1677.9 (s), 1449.2 (m), 1342.4 (s), 1254.5 (s), 1198.4 (s), 1084.8 (m), 1047.4 (m), 863.1 (m), 733.3 (s), 690.8 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 364.1059, Obs. 364.1064.

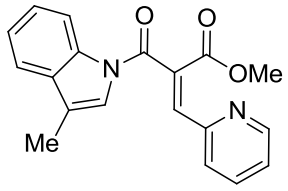


(*Z*)-Methyl 3-(furan-2-yl)-2-(3-methyl-1*H*-indole-1-carbonyl)acrylate (IV-35f): Methyl 3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.330 g, 1.44 mmol), furan-2-carbaldehyde (0.173 g, 1.80 mmol), glacial acetic acid (0.40 mL, 0.576 mmol), piperidine (0.10 mL, 0.0144 mmol) and benzene (30 mL) were mixed according to general method A to yield **IV-35f** as a light brown solid (0.210 g, 47%) after 12 h. R_f 0.30-0.35 (20% EtOAc/Hex). [**m.p.** 142-144 °C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.58 (d, *J* = 8.1 Hz, 1H), 7.66 (s, 1H), 7.47 – 7.17 (m, 4H), 6.89 (s, 1H), 6.66 (d, *J* = 3.5 Hz, 1H), 6.30 (d, *J* = 1.7 Hz, 1H), 3.71 (s, 3H), 2.13 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 164.7, 164.2, 148.6, 146.9, 135.5, 132.0, 128.8, 125.2, 123.9, 122.6, 122.2, 118.8, 118.7, 118.5, 116.8, 112.6, 52.7, 9.6. **IR**: 3126.6 (w), 2947.2 (w), 3053.5 (w), 2910.7 (w), 1710.1 (s), 1688.1 (s), 1629.7 (s), 1448.6 (s), 1433.8 (s), 1390.9 (s), 1376.5 (m), 1247.9 (s), 1227.1 (s), 1204.3 (s), 1047.4 (m), 1017.5 (m), 877.6 (m), 731.1 (s), 700.9 (m), 590.1 (m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 309.1001, Obs. 309.0998.



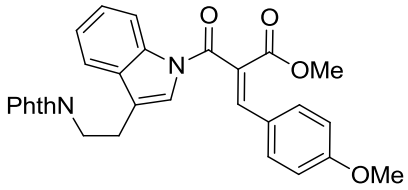
(*Z*)-Methyl 2-(3-methyl-1*H*-indole-1-carbonyl)-3-(thiophen-2-yl)acrylate (IV-35g): Methyl 3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.500 g, 2.16 mmol), thiophene-2-carbaldehyde (0.303 g, 2.70 mmol), glacial acetic acid (0.0520 g, 0.867 mmol), piperidine (0.184 g, 0.216 mmol) and benzene (30 mL) were combined according to general method A to afford **IV-35g** as a white solid (0.371 g, 53%) after 12 h. R_f 0.30-0.35 (20% EtOAc/Hex). [**m.p.** 128-130 °C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.68 (d, *J* =

8.0 Hz, 1H), 8.10 (s, 1H), 7.56 – 7.31 (m, 5H), 7.03 – 6.95 (m, 2H), 3.81 (s, 3H), 2.20 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 164.7, 164.2, 135.8, 135.4, 134.3, 132.4, 132.1, 128.0, 125.4, 124.2, 123.0, 122.2, 119.5, 118.8, 116.9, 52.7, 9.7. **IR**: 3103.3 (m), 3060.2 (m), 2910.7 (w), 2850.9 (w), 1710.3 (s), 1677.8 (s), 1604.7 (s), 1450.8 (s), 1418.1 (s), 1392.2 (s), 1345.9 (s), 1251.1 (s), 1200.1 (s), 1142.5 (m), 1044.6 (m), 964.6 (w), 880.2 (m), 759.3 (s), 711.2 (s), 613.0 (m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 325.0773, Obs. 325.0769.

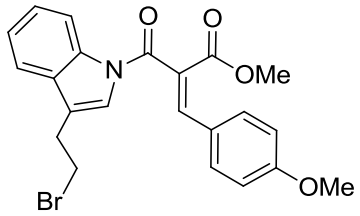


(*Z*)-Methyl 2-(3-methyl-1*H*-indole-1-carbonyl)-3-(pyridin-2-yl)acrylate (IV-35h): Methyl 3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.330 g, 1.44 mmol), picolinaldehyde (0.193 g, 1.80 mmol), glacial acetic acid (0.400 mL, 0.576 mmol), piperidine (0.100 mL, 0.144 mmol) and benzene (30 mL) were combined according to general method A to afford **IV-35h** as a white solid (0.250 g, 54%) after 12 h. R_f 0.30-0.35 (20% EtOAc/Hex). [**m.p.** 98-100 °C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.55 (d, *J* = 8.0 Hz, 1H), 8.20 – 8.15 (m, 1H), 7.80 (s, 1H), 7.62 – 7.49 (m, 1H), 7.44 – 7.10 (m, 4H), 7.07 – 6.97 (m, 1H), 6.84 (s, 1H), 3.72 (s, 3H), 2.07 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 164.7, 164.6, 150.6, 150.1, 140.8, 136.6, 135.6, 131.8, 129.3, 126.2, 125.0, 124.4, 123.5, 122.5, 118.6, 118.3, 116.7, 53.0, 9.7. **IR**: 3060.2 (w), 2940.6 (w), 2920.7 (w), 1721.8 (s), 1690.9 (s), 1678.7 (s), 1450.7 (s), 1433.4 (s), 1332.8 (m), 1262.9 (s), 1202.3 (s), 1087.5

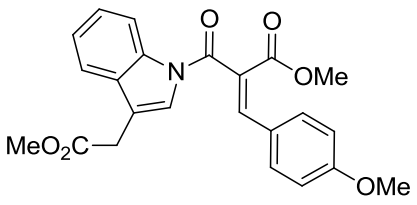
(m), 881.6 (m), 730.9 (s), 700.2 (s), 622.5 (m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 320.1161, Obs. 320.1162.



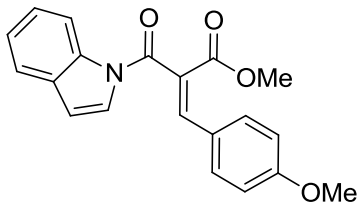
(*Z*)-Methyl 2-(3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-1*H*-indole-1-carbonyl)-3-(4-methoxyphenyl)acrylate (IV-35i): Methyl 3-(3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-1*H*-indol-1-yl)-3-oxopropanoate (1.08 g, 2.77 mmol), 4-methoxybenzaldehyde (0.459 g, 3.37 mmol), glacial acetic acid (0.0940 g, 1.57 mmol), piperidine (0.022 g, 0.253 mmol) and benzene (150 mL) were mixed according to general method A to yield **IV-35i** as a light yellow solid (0.569 g, 40%) after 16 h. R_f 0.40 (40% EtOAc/Hex). [**m.p.** 147-149 °C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.64 (d, *J* = 8.0 Hz, 1H), 7.92 (s, 1H), 7.78 – 7.72 (m, 2H), 7.71 – 7.64 (m, 3H), 7.48 – 7.31 (m, 4H), 7.13 (s, 1H), 6.79 – 6.71 (m, 2H), 3.95 – 3.88 (m, 2H), 3.77 (s, 3H), 3.74 (s, 3H), 3.05 – 2.96 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.1, 165.5, 164.9, 161.9, 143.3, 135.5, 133.9, 132.1, 131.9, 131.1, 125.6, 124.8, 124.4, 123.2, 122.9, 119.7, 118.9, 117.0, 114.6, 55.3, 52.7, 37.1, 24.1. **IR**: 3120.0 (w), 3060.2 (w), 2950.6 (w), 2844.3 (w), 1790.2 (s), 1691.8 (s), 1678.5 (s), 1652.9 (s), 1598.7 (s), 1434.3 (m), 1390.0 (s), 1256.0 (s), 1203.9 (s), 1172.7 (s), 1121.3 (m), 1019.5 (m), 888.2 (m), 750.6 (m), 718.5 (s), 529.5 (m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 508.1634, Obs. 508.1638.



(*Z*)-Methyl 2-(3-(2-bromoethyl)-1*H*-indole-1-carbonyl)-3-(4-methoxyphenyl)acrylate (IV-35j): Methyl 3-(3-(2-bromoethyl)-1*H*-indol-1-yl)-3-oxopropanoate (0.345 g, 1.06 mmol), 4-methoxybenzaldehyde (0.244 g, 1.64 mmol), glacial acetic acid (0.0315 g, 0.524 mmol), piperidine (0.0172 g, 0.202 mmol) and benzene (30 mL) were combined according to general method A to afford **IV-35j** as a yellowish orange solid (0.384 g, 82%) after 14 h. R_f 0.31 (20% EtOAc/Hex). [**m.p.** 90-92 °C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.67 (d, *J* = 8.0 Hz, 1H), 7.94 (s, 1H), 7.55 – 7.42 (m, 2H), 7.42 – 7.34 (m, 3H), 7.07 (s, 1H), 6.79 – 6.73 (m, 2H), 3.80 (s, 3H), 3.75 (s, 3H), 3.66 (t, *J* = 7.2 Hz, 1H), 3.52 (t, *J* = 7.3 Hz, 1H), 3.16 (t, *J* = 7.3 Hz, 1H), 3.06 (t, *J* = 7.1 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.5, 165.0, 162.0, 143.6, 135.5, 132.1, 130.6, 125.7, 124.7, 124.3, 123.6, 123.4, 123.2, 120.3, 118.5, 117.2, 114.7, 77.2, 55.4, 52.8, 43.1, 31.0, 28.7, 28.5. **IR**: 3060.2 (w), 3007.0 (w), 2957.2 (w), 2834.3 (w), 1708.5 (m), 1691.0 (m), 1598.9 (s), 1512.2 (m), 1450.9 (m), 1392.8 (m), 1256.3 (s), 1203.1 (s), 1172.6 (s), 1026.8 (m), 878.2 (w), 830.6 (m), 730.4 (s), 700.6 (s), 539.5 (m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 441.0576, Obs. 441.0580.

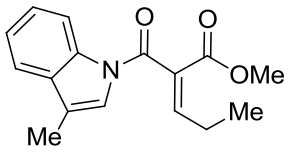


(*Z*)-Methyl 2-(3-(2-methoxy-2-oxoethyl)-1*H*-indole-1-carbonyl)-3-(4-methoxyphenyl) acrylate (IV-35k): Methyl 3-(3-(2-methoxy-2-oxoethyl)-1*H*-indol-1-yl)-3-oxopropanoate (1.01 g, 3.50 mmol), 4-methoxybenzaldehyde (0.615 g, 4.52 mmol), glacial acetic acid (0.105 g, 1.75 mmol), piperidine (0.043 g, 0.506 mmol) and benzene (150 mL) were combined according to general method A to afford **IV-35k** as a light yellow solid (0.568 g, 40%) after 16 h. R_f 0.26 (40% EtOAc/Hex). [**m.p.** 147-149 °C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.66 (d, *J* = 8.1 Hz, 1H), 7.93 (s, 1H), 7.57 – 7.42 (m, 3H), 7.42 – 7.33 (m, 2H), 7.20 (s, 1H), 6.80 – 6.74 (m, 2H), 3.80 (s, 3H), 3.74 (s, 3H), 3.65 (s, 3H), 3.63 (s, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.8, 165.6, 164.9, 161.9, 143.5, 135.4, 132.1, 130.8, 125.6, 124.7, 124.4, 124.2, 123.1, 119.0, 117.0, 115.8, 114.6, 55.3, 52.8, 52.1, 30.7. **IR**: 3050.2 (w), 3003.7 (w), 2953.9 (w), 2841.0 (w), 1737.6 (m), 1722.3 (m), 1710.6 (m), 1691.1 (m), 1598.9 (s), 1512.4 (m), 1450.7 (m), 1392.8 (m), 1256.2 (s), 1202.3 (m), 1172.0 (s), 1045.5 (m), 1026.7 (m), 888.2 (w), 730.4 (s), 700.4 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 407.1369, Obs. 407.1389.



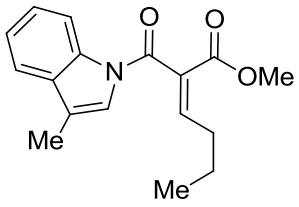
(*Z*)-Methyl 2-(1*H*-indole-1-carbonyl)-3-(4-methoxyphenyl)acrylate (IV-35l): Methyl 3-(1*H*-indol-1-yl)-3-oxopropanoate (0.194 g, 0.897 mmol), 4-methoxybenzaldehyde (0.159 g, 1.17 mmol), glacial acetic acid (0.0248 g, 0.413 mmol), piperidine (0.0766 g, 0.897 mmol) and benzene (10 mL) were combined according to general method A to afford **IV-35l** as a white solid (0.260 g, 86%) after 12 h. R_f 0.40 (20% EtOAc/Hex). [**m.p.**

86-88 °C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.70 (d, *J* = 8.8 Hz, 1H), 7.95 (s, 1H), 7.57 (d, *J* = 7.3 Hz, 1H), 7.50 – 7.29 (m, 4H), 7.21 (d, *J* = 3.8 Hz, 1H), 6.81 – 6.71 (m, 2H), 6.54 (d, *J* = 3.7 Hz, 1H), 3.79 (s, 3H), 3.72 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.8, 164.9, 161.9, 143.4, 135.1, 132.0, 131.0, 125.8, 125.2, 124.6, 124.4, 123.1, 120.9, 120.8 (2), 116.8, 114.6, 109.9, 55.2, 52.7. **IR**: 3139.9 (w), 3046.9 (w), 2940.6 (w), 2834.3 (w), 1708.5 (s), 1691.0 (s), 1597.9 (s), 1511.8 (s), 1449.3 (m), 1389.1 (m), 1253.7 (s), 1221.6 (m), 1170.7 (m), 1113.3 (m), 1054.2 (m), 887.6 (m), 749.7 (s), 727.5 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 335.1158, Obs. 335.1155.

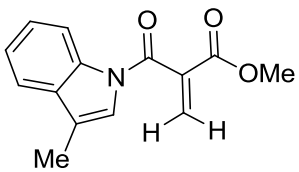


(*Z*)-Methyl 2-(3-methyl-1*H*-indole-1-carbonyl)pent-2-enoate (IV-35m): Methyl 3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.500 g, 2.16 mmol), propionaldehyde (0.155 mL, 2.16 mmol), $TiCl_4$•THF (1.44 g, 4.32 mmol), CCl_4 (0.417 mL, 4.32 mmol), pyridine (0.700 mL, 8.65 mmol) and THF (35 mL) were combined according to general method B to yield **IV-35m** as a white solid (0.410 g, 66%) after 14 h. R_f 0.70 (20% EtOAc/Hex). [**m.p.** 104-106 °C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.56 (d, *J* = 7.5 Hz, 1H), 7.51 (d, *J* = 8.2 Hz, 1H), 7.45 – 7.30 (m, 2H), 7.26 – 7.17 (m, 1H), 6.94 (s, 1H), 3.75 (s, 3H), 2.31 – 2.15 (m, 5H), 1.08 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 164.0, 150.5, 135.5, 131.9, 129.4, 125.3, 124.0, 122.4, 122.1, 119.1, 118.8, 116.7, 52.5, 23.3, 12.5, 9.6. **IR**: 3053.5 (w), 2967.2 (w), 2953.9 (w), 2870.9 (w), 1725.2 (s), 1690.6 (s), 1652.6 (s), 1643.2 (m), 1450.9 (s), 1392.0 (s), 1330.1 (s), 1264.5 (m), 1212.6 (s), 1149.9 (m), 1047.8 (m),

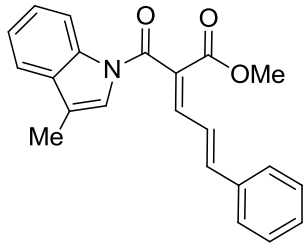
874.0 (m), 745.4 (s), 701.4 (m), 625.4 (w) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 271.1208, Obs. 271.1214.



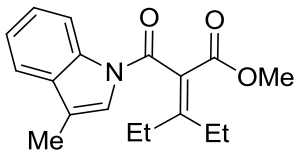
(*Z*)-Methyl 2-(3-methyl-1*H*-indole-1-carbonyl)hex-2-enoate (IV-35n): Methyl 3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.500 g, 2.16 mmol), butyraldehyde (0.194 mL, 2.16 mmol), $TiCl_4$•THF (1.44 g, 4.32 mmol), CCl_4 (0.417 mL, 4.32 mmol), pyridine (0.700 mL, 8.65 mmol) and THF (35 mL) were mixed according to general method B to afford **IV-35n** as yellow oil (0.442 g, 68%) after 14 h. R_f 0.70 (20% EtOAc/Hex). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.56 (d, *J* = 7.9 Hz, 1H), 7.51 (d, *J* = 8.2 Hz, 1H), 7.45 – 7.18 (m, 3H), 6.93 (s, 1H), 3.75 (s, 3H), 2.25 (s, 3H), 2.18 (q, *J* = 15.0, 7.5 Hz, 2H), 1.58 – 1.43 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 164.0, 149.3, 135.5, 131.9, 130.0, 125.2, 124.0, 122.5, 119.0, 118.8, 116.8, 52.5, 31.8, 21.4, 13.7, 9.6. **IR**: 3056.8 (w), 2963.8 (m), 2930.6 (w), 2867.5 (w), 1725.2 (s), 1691.0 (s), 1679.0 (s), 1450.9 (s), 1392.6 (s), 1340.6 (m), 1329.1 (w), 1248.9 (s), 1212.4 (s), 1078.7 (m), 1039.4 (w), 951.3 (w), 732.6 (s), 701.4 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 285.1365, Obs. 285.1365.



Methyl 2-(3-methyl-1*H*-indole-1-carbonyl)acrylate (IV-35o): Using conditions established by Yiotakis:[24] A round bottom flask was charged with acetic acid (12 mL), methyl 3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.602 g, 2.60 mmol), formaldehyde (0.0708 g, 2.359 mmol), and $Cu(OAc)_2$ (0.0416 g, 0.229 mmol) and the mixture was heated at reflux for 3 h. The solvent was removed *in vacuo* and diethyl ether was added. The mixture was filtered and the filtrate was washed successively with 1 M HCl, dilute $NaHCO_3$, 1 M HCl, and brine. The organics were dried with Na_2SO_4 and concentrated under reduced pressure. The residue was purified using silica gel flash chromatography to yield **IV-35o** as a brown oil (0.470 g, 74%). R_f 0.37 (20% EtOAc/Hex). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.44 (d, *J* = 7.3 Hz, 1H), 7.56 – 7.49 (m, 1H), 7.44 – 7.30 (m, 2H), 6.99 (s, 1H), 6.79 (d, *J* = 0.4 Hz, 1H), 6.15 (s, 1H), 3.81 (d, *J* = 0.8 Hz, 3H), 2.27 – 2.25 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.8, 163.6, 137.3, 135.7, 132.0, 131.7, 125.4, 124.1, 122.7, 119.2, 119.0, 116.6, 52.8, 9.7. **IR**: 3119.9 (w), 3060.2 (w), 2960.5 (w), 2914.0 (w), 1736.9 (s), 1728.1 (s), 1690.8 (s), 1678.3 (s), 1449.6 (s), 1387.6 (m), 1343.5 (m), 1235.7 (m), 1170.7 (m), 1151.2 (m), 1061.6 (m), 931.4 (w), 881.6 (m), 735.1 (s), 701.4 (m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 243.0895, Obs. 243.0891.

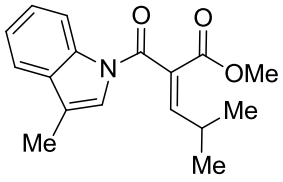


(2*Z*,4*E*)-Methyl 2-(3-methyl-1*H*-indole-1-carbonyl)-5-phenylpenta-2,4-dienoate (IV-35p): Methyl 3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.201 g, 0.868 mmol), cinnamaldehyde (0.158 g, 1.19 mmol), glacial acetic acid (0.0525 g, 0.873 mmol), piperidine (0.0259 g, 0.304 mmol) and benzene (15 mL) were combined according to general method A to yield **IV-35p** as a red solid (0.280 g, 93%) after 12 h. R_f 0.40 (20% EtOAc/Hex). [**m.p.** 108-110 °C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.65 (s, 1H), 7.76 (d, *J* = 11.8 Hz, 1H), 7.58 – 7.52 (m, 1H), 7.49 – 7.27 (m, 7H), 7.12 (d, *J* = 15.3 Hz, 1H), 6.97 (s, 1H), 6.89 – 6.76 (m, 1H), 3.79 (s, 3H), 2.25 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) (Isomers!) δ 164.6, 145.0, 144.2, 135.6, 135.1, 132.1, 130.0, 128.8, 127.8, 126.7, 125.3, 124.1, 122.8, 122.2, 119.2, 119.0,116.8, 52.6, 34.5, 31.5, 25.1, 22.5, 14.1, 9.7. **IR**: 3123.3 (w), 3036.9 (w), 2953.9 (w), 2841.0 (w), 1710.8 (s), 1720.8 (s), 1678.1 (s), 1611.5 (s), 1589.9 (s), 1434.0 (s), 1392.4 (m), 1340.6 (m), 1236.3 (s), 1210.4 (s), 1154.0 (m), 1080.2 (m), 1047.9 (m), 974.9 (w), 888.2 (w), 746.8 (s), 689.0 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 345.1365, Obs. 345.1367.



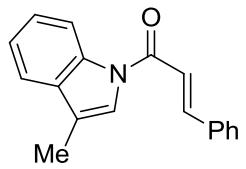
Methyl 3-ethyl-2-(3-methyl-1*H*-indole-1-carbonyl)pent-2-enoate (IV-35q): Methyl 3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.800 g, 3.46 mmol), pentan-3-one (0.372 mL, 3.46 mmol), $TiCl_4$•THF (2.31 g, 6.92 mmol), CCl_4 (0.669 mL, 6.92 mmol), pyridine (1.12 mL, 13.8 mmol) and THF (20 mL) were combined according to general method B to yield **IV-35q** as a white solid (0.642 g, 62%) after 12 h. R_f 0.50 (15% EtOAc/Hex). [**m.p.** 109-111 °C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.52 (d, *J* = 7.6 Hz, 1H),

7.43 – 7.29 (m, 2H), 6.98 (s, 1H), 3.66 (s, 3H), 2.78 (q, *J* = 7.5 Hz, 2H), 2.26 (d, *J* = 1.3 Hz, 3H), 2.18 (q, *J* = 7.5 Hz, 2H), 1.24 (t, *J* = 7.3 Hz, 3H), 1.06 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.9, 163.9, 135.6, 131.9, 125.1, 124.6, 123.8, 122.6, 118.9, 118.6, 116.7, 52.0, 28.7, 25.1, 12.8, 12.2, 9.7. **IR**: 2970.5 (w), 2943.9 (w), 2867.5 (w), 1723.0 (s), 1678.6 (s), 1632.1 (m), 1451.9 (m), 1367.6 (m), 1347.1 (m), 1213.8 (s), 1124.0 (w), 838.4 (m), 767.3 (s), 753.5 (s), 672.3 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 299.1521, Obs. 299.1522.



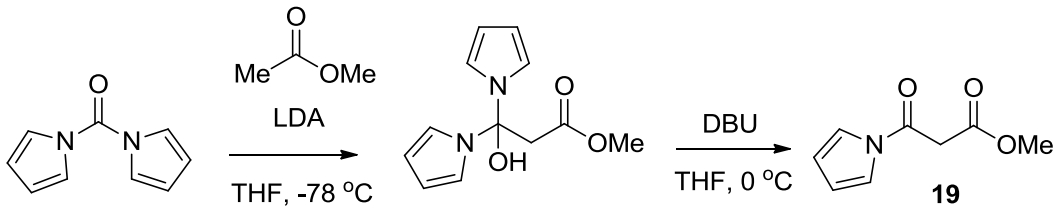
(*Z*)-Methyl 4-methyl-2-(3-methyl-1*H*-indole-1-carbonyl)pent-2-enoate (IV-35r): Methyl 3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate (1.06 g, 4.58 mmol), isobutyraldehyde (0.429 g, 5.95 mmol), glacial acetic acid (0.126 g, 2.10 mmol), piperidine (0.389 g, 4.58 mmol) and benzene (25 mL) were combined according to general method A to afford **IV-35r** as a white solid (1.24 g, 95%) after 12 h. R_f 0.4 (15% EtOAc/Hex). [**m.p.** 128-130 °C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.58 (d, *J* = 8.0 Hz, 1H), 7.55 – 7.49 (m, 1H), 7.45 – 7.30 (m, 2H), 7.11 – 6.92 (m, 2H), 3.75 (s, 3H), 2.71 – 2.40 (m, 1H), 2.27 (s, 3H), 1.07 (d, *J* = 6.7 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 164.1, 163.9, 154.7, 135.5, 131.8, 127.6, 125.2, 124.0, 122.5, 118.9, 118.8, 116.6, 52.4, 29.6, 21.4, 9.5. **IR**: 3113.3 (w), 2953.9 (m), 2930.6 (w), 2874.2 (w), 1725.2 (s), 1690.7 (s), 1679.8 (s), 1652.6 (m), 1449.8 (s), 1392.6 (s), 1340.7 (s), 1331.4 (m), 1243.5 (s), 1227.9

(s), 1190.9 (m), 1153.6 (m), 1043.5 (m), 888.2 (m), 759.2 (s), 747.4 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 285.1365, Obs. 285.1361.



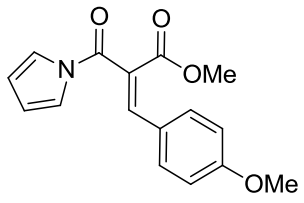
(*E*)-1-(3-methyl-1*H*-indol-1-yl)-3-phenylprop-2-en-1-one (IV-35s): Sodium hydride (0.186 g, 4.64 mmol) was suspended in THF (20 mL) and cooled to 0 °C. In a separate flask, 3-methyl-1*H*-indole (0.487 g, 3.72 mmol) was dissolved in THF (5 mL) and syringed into the basic solution. After 30 min, cinnamoyl chloride (3.37 mmol) in THF (5 mL) was slowly added. The reaction was stirred for 12 h at room temperature then quenched with water. The organic layer was separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography to afford **IV-35s** as a yellow-orange oil (0.617 g, 70%). (15% EtOAc/Hex, R_f 0.50) **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.61 (d, *J* = 7.7 Hz, 1H), 7.98 (d, *J* = 15.5 Hz, 1H), 7.68 – 7.58 (m, 2H), 7.57 – 7.51 (m, 1H), 7.46 – 7.31 (m, 6H), 7.20 (d, *J* = 15.4 Hz, 1H), 2.32 (dd, *J* = 1.3, 0.6 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.6, 145.7, 136.0, 134.3, 131.4, 130.4, 128.8, 128.1, 124.9, 123.4, 121.4, 118.7, 118.2, 117.3, 116.7, 9.6. **IR**: 3060.2 (w), 3023.6 (w), 2920.7 (w), 1677.4 (s), 1665.9 (s), 1619.7 (s), 1613.2 (s), 1575.7 (m), 1445.8 (s), 1387.1 (s), 1372.2 (s), 1346.9 (s), 1298.6 (s), 1229.5 (s), 1199.5 (s), 1119.3 (m), 1066.2 (s), 963.0 (m), 848.3 (m), 755.8 (s), 731.0 (s), 698.6 (s), 678.5 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 261.1154, Obs. 261.1157.

Preparation of (*Z*)-Methyl 3-(4-methoxyphenyl)-2-(1*H*-pyrrole-1-carbonyl)acrylate (IV-38):



Methyl 3-oxo-3-(1*H*-pyrrol-1-yl)propanoate (19): Following a modification of Evans' reported procedure:[25] *n*-BuLi (10M in hexanes, 36 mmol) was added to a solution of diisopropylamine (3.13 mL, 22.16 mmol) in THF (40 mL) at -78°C. After 30 min, methyl acetate (2.9 mL, 36.5 mmol) was added slowly and the mixture was stirred for another 30 min. A solution of di(1*H*-pyrrol-1-yl)methanone[26] (3.55 g, 22.16 mmol) in THF (10 mL) was added to the reaction vessel. After 1 h, the reaction was quenched with AcOH and washed with saturated $NaHCO_3$. The organic layer was separated, and the aqueous layer was washed with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude product was dissolved in THF, and 1,8-diazabicyclo[5.4.0]undec-7-ene (500 µL, 3.34 mmol) was added. After 1 h, EtOAc was added to the reaction flask. The mixture was washed with 0.5M $CuSO_4$, washed with brine, dried over Na_2SO_4, filtered, concentrated, and purified to afford **19** as a brown oil (2.92g, 79%). R_f 0.28 (20% EtOAc/Hex). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.23 (s, 2H), 6.31 – 6.22 (m, 2H), 3.83 (s, 2H), 3.70 (s, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.2, 163.1, 119.1, 113.7, 52.6, 41.8. **IR**: 3143.2 (w), 3000.4 (w), 2950.6 (w), 1742.1 (s), 1709.9 (s), 1469.4 (m), 1343.4 (s), 1249.2 (s), 1208.0 (m), 1160.0 (m), 1115.1 (s), 1076.0

(m), 994.5 (m), 917.8 (s), 738.5 (s), 675.7 (m), 610.0 (m), 597.7 (m), 519.6 (m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 167.0582, Obs. 167.0596.



(*Z*)-Methyl 3-(4-methoxyphenyl)-2-(1*H*-pyrrole-1-carbonyl)acrylate (IV-38): Methyl 3-oxo-3-(1*H*-pyrrol-1-yl)propanoate (0.500 g, 2.99 mmol), 4-methoxybenzaldehyde (0.560 g, 4.11 mmol), glacial acetic acid (0.105 g, 1.75 mmol), piperidine (0.0431 g, 0.506 mmol) and benzene (25 mL) were combined according to general method A to afford **IV-38** as a brown solid (0.780 g, 91%) after 12 h. R_f 0.25 (20% EtOAc/Hex). [**m.p.** 79-81 °C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.37 – 7.29 (m, 3H), 6.85 – 6.78 (m, 3H), 6.27 (s, 2H), 3.80 (s, 3H), 3.78 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.2, 164.7, 162.0, 144.0, 132.0, 124.6, 122.3, 114.6, 114.1, 55.3, 52.8. **IR**: 3143.2 (w), 3073.4 (w), 2960.5 (w), 2837.6 (w), 1709.6 (s), 1678.6 (s), 1598.3 (s), 1512.6 (s), 1451.8 (m), 1288.9 (m), 1253.2 (m), 1202.3 (m), 1173.4 (s), 1126.4 (m), 1069.3 (m), 1017.7 (m), 884.9 (m), 825.1 (m), 730.3 (s), 700.5 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 285.1001, Obs. 285.0997

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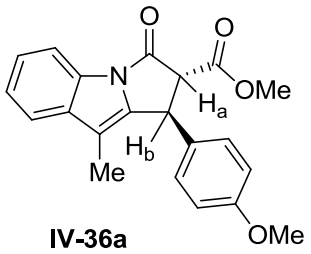
4.5.3. $In(OTf)_3$-Catalyzed Cyclizations IV36a-r, IV-37, and IV-39

General Procedure: To a mixture of $In(OTf)_3$ (0.10 equiv) in DCE or toluene heated to a reflux, a solution of acrylates **IV-35** (1.0 equiv) in solvent was syringed into the reaction vessel. The reaction was monitored by TLC and quenched with water. The phases were separated, and the product was extracted from the aqueous phase with DCM. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated for column chromatography using silica gel.

Rationale for cis-trans assigment: The major diastereomer is *trans* in spatial orientation based on a correlation between the calculated dihedral angle between H_a and H_b for both the *cis*- and *trans*-isomers and the expected Karplus coupling constant. This value was then compared to the experimental value using ^1H NMR (Table 4.5). Diastereomeric ratios are reported where applicable, and the integral value for each signal is noted.

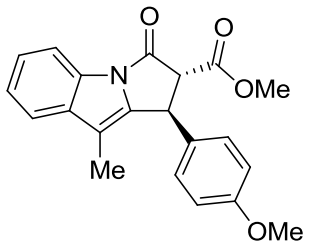


IV-36a

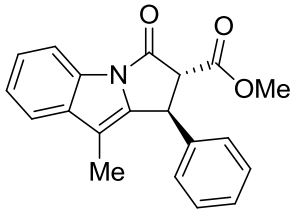
Table 4.5. Assignment of *cis/trans* Orientation Based on Dihedral Angles and Observed *J*-Values

Diastereomer	Dihedral Angle[a]	Predicted Karplus J-value (Hz)[b]	Observed J-value (Hz)[c]
cis	8.5°	~ 7-8	9-10
trans	125.8°	~ 5-6	5-6

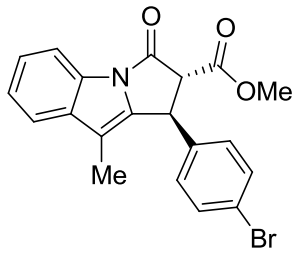
[a] Determined from energy minimizations using Trident software from Schrodinger, Inc. [b] Determined from Karplus coupling constant chart[27]
[c] Determined by ^1H NMR spectroscopy



Methyl 1-(4-methoxyphenyl)-9-methyl-3-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-2-carboxylate (IV-36a): (*Z*)-Methyl 3-(4-methoxyphenyl)-2-(3-methyl-1*H*-indole-1-carbonyl)acrylate (0.070 g, 0.200 mmol), $In(OTf)_3$ (0.0112 g, 0.0200 mmol) and 1,2-DCE (5 mL) were combined according to the general procedure to afford **IV-36a** as an orange oil (0.0666 g, 95%) after 2 h. R_f 0.40 (20% EtOAc/Hex). *Diastereomeric ratio*: (15:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.10 – 8.01 (m, 1.13), 7.50 – 7.42 (m, 1.22), 7.38 – 7.30 (m, 2.22), 7.22 – 7.15 (m, 2.02), 6.92 – 6.85 (m, 2.08), 5.01 (d, *J* = 4.7 Hz, 1.04), 4.46 (d, *J* = 9.8 Hz, 0.05), 4.00 (d, *J* = 5.3 Hz, 0.93), 3.86 (s, 3.00), 3.81 (s, 4.28), 3.26 (s, 0.16), 1.93 (s, 3.14). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.2, 164.5, 159.1, 138.8, 136.4, 131.3, 130.2, 128.5, 124.4, 124.0, 122.2, 118.9, 114.5, 113.9, 110.8, 63.0, 55.3, 53.2, 42.0, 8.1. **IR**: 3000.4 (w), 2950.6 (w), 2920.7 (w), 2834.3 (w), 1737.3 (s), 1726.3 (s), 1512.5 (m), 1453.7 (m), 1396.6 (m), 1311.3 (m), 1247.6 (s), 1176.7 (m), 1127.3 (w), 1031.6 (m), 828.4 (m), 749.4 (m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 349.1314, Obs. 349.1317.

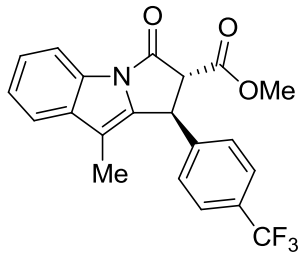


Methyl 9-methyl-3-oxo-1-phenyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-2-carboxylate (IV-36b): (*Z*)-Methyl 2-(3-methyl-1*H*-indole-1-carbonyl)-3-phenylacrylate (0.0750 g, 0.225 mmol), $In(OTf)_3$ (0.0126 g, 0.0224 mmol) and 1,2-DCE (5 mL) were mixed according to the general procedure to yield **IV-36b** as a pale yellow solid (0.0726 g, 97%) after 1 h. R_f 0.50 (15% EtOAc/Hex). *Diastereomeric ratio*: (16:1). [**m.p.** 95-97 °C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.10 – 8.03 (m, 1.10), 7.49 – 7.44 (m, 1.27), 7.42 – 7.30 (m, 5.93), 7.28 – 7.23 (m, 3.14), 5.05 (d, *J* = 5.2 Hz, 1.12), 4.50 (d, *J* = 9.8 Hz, 0.06), 4.03 (d, *J* = 5.3 Hz, 0.97), 3.88 – 3.84 (m, 3.51), 3.20 (s, 0.22), 1.98 – 1.91 (m, 3.37). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.1, 164.4, 139.4, 138.5, 136.4, 130.4, 129.2, 127.9, 127.5, 124.4, 124.1, 122.1, 119.0, 113.9, 111.0, 62.8, 53.3, 42.6, 8.2. **IR**: 3063.5 (w), 3026.9 (w), 2950.6 (w), 2917.3 (w), 2874.2 (w), 1737.2 (s), 1725.6 (s), 1635.4 (m), 1452.1 (s), 1396.0 (m), 1310.8 (w), 1161.8 (s), 954.6 (w), 771.9 (s), 747.3 (s), 699.3 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 319.1208, Obs. 319.1210.



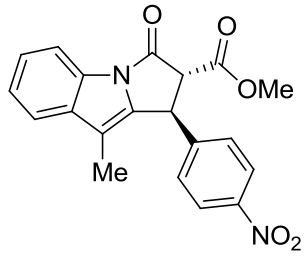
Methyl 1-(4-bromophenyl)-9-methyl-3-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-2-carboxylate (IV-36c): (*Z*)-Methyl 3-(4-bromophenyl)-2-(3-methyl-1*H*-indole-1-carbonyl)acrylate (0.075 g, 0.188 mmol), $In(OTf)_3$ (0.0106 g, 0.0188 mmol) and 1,2-DCE (4 mL) were combined according to the general procedure to afford **IV-36c** as a colorless oil (0.0696 g, 93%) after 14 h. R_f 0.40 (20% EtOAc/Hex). *Diastereomeric ratio*: (16:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.14 – 8.02 (m, 1.12), 7.54 – 7.43 (m, 3.42), 7.39 – 7.30 (m, 2.17), 7.19 – 7.07 (m, 2.09), 5.06 – 4.93 (m, 1.08), 4.48 (d, *J* = 9.9 Hz,

0.07), 3.98 (d, *J* = 5.4 Hz, 1.00), 3.87 (s, 3.12), 3.27 (s, 0.18), 1.94 (d, *J* = 1.3 Hz, 3.29). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.8, 164.0, 138.3, 137.7, 136.3, 132.3, 131.7, 130.2, 129.2, 124.5, 124.2, 121.8, 119.0, 113.9, 111.2, 62.5, 53.3, 42.0, 8.2. **IR**: 3056.8 (w), 2957.2 (w), 2910.7 (w), 2850.9 (w), 1736.9 (s), 1725.9 (s), 1635.4 (m), 1452.7 (m), 1435.1 (m), 1378.8 (m), 1251.1 (m), 1163.3 (m), 1132.5 (w), 1009.4 (m), 961.3 (w), 820.9 (w), 768.3 (m), 734.5 (m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 397.0314, Obs. 397.0308.

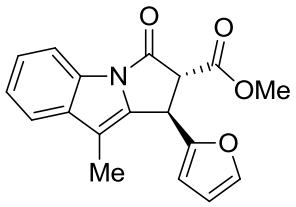


Methyl 9-methyl-3-oxo-1-(4-(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-2-carboxylate (IV-36d): (*Z*)-Methyl 2-(3-methyl-1*H*-indole-1-carbonyl)-3-(4-(trifluoromethyl)phenyl)acrylate (0.075 g, 0.194 mmol), $In(OTf)_3$ (0.0109 g, 0.0194 mmol) and 1,2-DCE (4 mL) were combined according to the general procedure to afford **IV-36d** as a white solid (0.0686 g, 92%) after 14 h. R_f 0.40 (20% EtOAc/Hex). [**m.p.** 129-131 °C] *Diastereomeric ratio*: (20:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.11 – 8.04 (m, 1.05), 7.64 (d, *J* = 8.1 Hz, 2.19), 7.53 – 7.31 (m, 5.55), 5.14 (d, *J* = 5.3 Hz, 1.05), 4.53 (d, *J* = 9.9 Hz, 0.05), 4.00 (d, *J* = 5.4 Hz, 1.01), 3.88 (s, 3.12), 3.22 (s, 0.15), 1.94 (d, *J* = 1.4 Hz, 3.26). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.7, 163.8, 143.4, 137.3, 136.2, 130.3, 127.9, 126.2, 126.2, 124.6, 124.4, 119.1, 114.0, 111.4, 62.4, 53.4, 42.2, 8.3. **IR**: 3056.8 (w), 2947.2 (w), 2920.7 (w), 2860.9 (w), 1737.2 (s), 1726.6 (s), 1615.5 (w), 1453.6 (m),

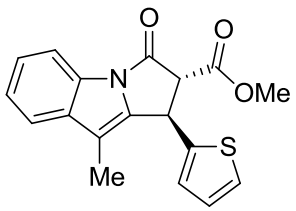
1396.9 (m), 1322.1 (s), 1251.4 (m), 1163.1 (s), 1123.0 (s), 1111.5 (s), 1067.4 (m), 1018.6 (m), 964.6 (w), 858.3 (m), 748.5 (m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 387.1082, Obs. 387.1093.



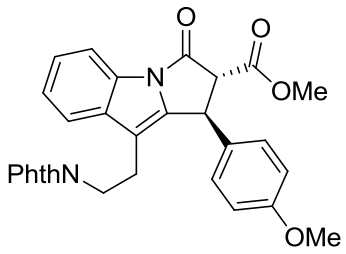
Methyl 9-methyl-1-(4-nitrophenyl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-2-carboxylate (IV-36e): 2-(3-Methyl-1*H*-indole-1-carbonyl)-3-(4-nitrophenyl)acrylate (0.100 g, 0.264 mmol), $In(OTf)_3$ (0.0148 g, 0.0264 mmol) and 1,2-DCE (6 mL) were combined according to the general procedure to afford **IV-36e** as a pale orange solid (0.0838 g, 84%) after 2.5 h. R_f 0.50 (15% EtOAc/Hex). [**m.p.** 141-143 °C] *Diastereomeric ratio*: (19:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.26 – 8.19 (m, 2.29), 8.08 – 8.03 (m, 1.09), 7.53 – 7.41 (m, 3.57), 7.41 – 7.33 (m, 2.34), 5.19 (d, *J* = 5.4 Hz, 1.15), 4.56 (d, *J* = 10.0 Hz, 0.05), 4.00 (d, *J* = 5.4 Hz, 1.00), 3.89 (s, 3.21), 3.26 (s, 0.19), 1.94 (d, *J* = 1.4 Hz, 3.41). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.5, 163.4, 147.5, 146.6, 136.7, 136.1, 130.3, 129.8, 128.5, 124.7, 124.5, 124.5, 123.6, 119.2, 113.9, 111.6, 62.1, 53.5, 42.0, 8.3. **IR**: 3063.5 (w), 2947.2 (w), 2914.0 (w), 2857.6 (w), 1737.1 (s), 1726.0 (s), 1598.9 (m), 1514.3 (m), 1453.2 (m), 1396.4 (m), 1344.2 (s), 1311.0 (m), 1250.1 (m), 1164.1 (m), 1132.7 (m), 1104.1 (m), 1021.0 (w), 971.2 (w), 856.6 (m), 732.7 (s), 697.8 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 364.1059, Obs. 364.1064.



Methyl 1-(furan-2-yl)-9-methyl-3-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-2-carboxylate (IV-36f): ((*Z*)-Methyl 3-(furan-2-yl)-2-(3-methyl-1*H*-indole-1-carbonyl)acrylate (0.075 g, 0.242 mmol), $In(OTf)_3$ (0.0136 g, 0.0242 mmol) and 1,2-DCE (4 mL) were combined according to the general procedure to afford **IV-36f** as a pale yellow oil (0.0726 g, 97%) after 2 h. R_f 0.40 (20% EtOAc/Hex). *Diastereomeric ratio*: (18:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.08 – 8.01 (m, 1.12), 7.51 – 7.43 (m, 1.18), 7.41 – 7.38 (m, 1.12), 7.37 – 7.29 (m, 2.32), 6.37 – 6.31 (m, 1.10), 6.27 – 6.21 (m, 1.11), 5.17 (d, *J* = 4.9 Hz, 1.08), 4.45 (d, *J* = 9.5 Hz, 0.05), 4.24 (d, *J* = 4.9 Hz, 1.00), 3.88 (s, 3.32), 3.48 (s, 0.15), 2.09 (d, *J* = 1.3 Hz, 3.40). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.8, 163.9, 150.9, 142.8, 136.3, 135.8, 130.2, 124.4, 124.2, 119.0, 113.9, 111.3, 110.4, 107.4, 59.2, 53.3, 36.0, 8.1. **IR**: 3079.0 (w), 2953.9 (w), 2910.7 (w), 2841.0 (w), 1737.4 (s), 1725.9 (s), 1711.3 (s), 1598.9 (w), 1453.4 (m), 1379.8 (m), 1310.4 (w), 1263.0 (m), 1124.9 (w), 1074.2 (w), 1010.4 (m), 795.2 (m), 731.6 (s), 700.9 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 309.1001, Obs. 309.1003.

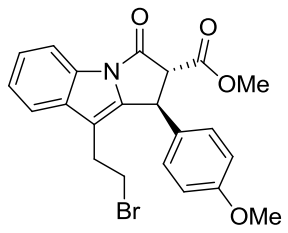


Methyl 9-methyl-3-oxo-1-(thiophen-2-yl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-2-carboxylate (IV-36g): (*Z*)-Methyl 2-(3-methyl-1*H*-indole-1-carbonyl)-3-(thiophen-2-yl)acrylate (0.075 g, 0.230 mmol), $In(OTf)_3$ (0.0129 g, 0.0230 mmol) and 1,2-DCE (4 mL) were combined according to the general procedure to afford **IV-36g** as a pale yellow solid (0.0737 g, 98%) after 2 h. R_f 0.40 (20% EtOAc/Hex). [**m.p.** 132-134 °C] *Diastereomeric ratio*: (24:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.08 – 8.03 (m, 1.11), 7.51 – 7.45 (m, 1.27), 7.39 – 7.31 (m, 2.40), 7.28 – 7.24 (m, 1.12), 7.03 – 6.96 (m, 2.18), 5.38 (d, *J* = 5.2 Hz, 1.03), 4.47 (d, *J* = 9.6 Hz, 0.04), 4.11 (d, *J* = 5.3 Hz, 1.00), 3.88 (s, 3.22), 3.39 (s, 0.14), 2.05 (d, *J* = 1.3 Hz, 3.38). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.7, 163.7, 142.1, 137.7, 136.3, 130.1, 127.1, 125.8, 125.3, 124.4, 124.3, 119.1, 113.9, 111.5, 63.2, 53.3, 37.7, 8.4. **IR**: 3055.8 (w), 2953.1 (w), 2920.2 (w), 2859.2 (w), 1729.1 (s), 1631.9 (m), 1455.2 (s), 1396.5 (m), 1379.1 (m), 1312.2 (m), 1252.2 (m), 1161.1 (m), 1132.7 (m), 1062.9 (w), 961.5 (w), 845.0 (w), 748.5 (s), 701.7 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 325.0773, Obs. 325.0781.



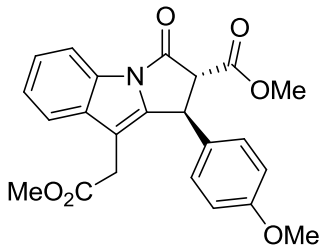
Methyl 9-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-1-(4-methoxyphenyl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-2-carboxylate (IV-36i): (*Z*)-Methyl 2-(3-(2-(1,3-dioxoisoindolin-2-yl)ethyl)-1*H*-indole-1-carbonyl)-3-(4-methoxyphenyl)acrylate (0.075 g, 0.147 mmol), $In(OTf)_3$ (0.00828 g, 0.0147 mmol) and 1,2-DCE (5 mL) were combined according to the general procedure to afford **IV-36i** as a light yellow solid (0.0721 g,

96%) after 4 h. R_f 0.30 (20% EtOAc/Hex). [**m.p.** 142-144 °C] *Diastereomeric ratio*: (14:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.12 – 8.01 (m, 1.06), 7.81 – 7.72 (m, 2.13), 7.72 – 7.56 (m, 3.28), 7.34 – 7.16 (m, 4.43), 6.92 – 6.83 (m, 2.12), 5.09 – 4.97 (m, 1.05), 4.46 (d, *J* = 9.8 Hz, 0.07), 4.03 (d, *J* = 5.2 Hz, 1.00), 3.86 – 3.76 (m, 6.11), 3.76 – 3.57 (m, 2.36), 3.27 (s, 0.21), 2.88 – 2.75 (m, 1.13), 2.70 – 2.56 (m, 1.08). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.9, 167.9, 164.7, 159.3, 140.7, 135.4, 133.9, 132.0, 131.1, 130.2, 128.6, 124.6, 124.2, 123.1, 119.1, 114.7, 114.0, 111.2, 62.7, 55.3, 53.2, 42.1, 36.9, 22.7. **IR**: 3050.2 (w), 2970.5 (w), 2841.0 (w), 1728.0 (s), 1709.5 (s), 1513.0 (m), 1456.8 (m), 1435.4 (m), 1391.0 (s), 1247.7 (s), 1178.0 (s), 1021.0 (s), 831.7 (m), 775.3 (m), 718.1 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 508.1634, Obs. 508.1631.



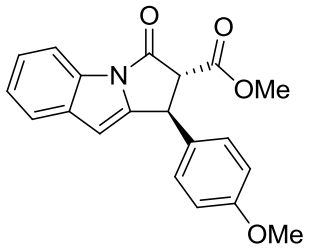
Methyl 9-(2-bromoethyl)-1-(4-methoxyphenyl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-2-carboxylate (IV-36j): (*Z*)-Methyl 2-(3-(2-bromoethyl)-1*H*-indole-1-carbonyl)-3-(4-methoxyphenyl)acrylate (0.061 g, 0.138 mmol), $In(OTf)_3$ (0.0081 g, 0.014 mmol) and 1,2-DCE (7 mL) were combined according to the general procedure to afford **IV-36j** as a brown oil (0.0418 g, 69%) after 12 h. R_f 0.24 (30% EtOAc/Hex). *Diastereomeric ratio*: (25:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.20 – 8.14 (m, 0.17), 8.12 – 8.06 (m, 0.95), 7.71 (s, 0.07), 7.52 – 7.44 (m, 1.30), 7.42 – 7.29 (m, 2.54), 7.21 – 7.14 (m, 2.08), 7.10 – 7.14 (m, 0.31), 6.93 – 6.80 (m, 2.44), 5.06 (d, *J* = 4.9 Hz, 1.00), 4.52 – 4.45 (m, 0.04), 4.06 – 4.01 (m, 0.98), 3.90 – 3.77 (m, 6.82), 3.56 – 3.21 (m, 3.42H), 3.12 –

2.64 (m, 3.54). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.8, 164.7, 159.4, 141.1, 140.9, 135.2, 135.0, 131.5, 131.1, 131.0, 130.2, 130.0, 128.3, 124.6, 124.3, 118.8, 114.7, 114.4, 114.2, 113.9, 112.2, 111.3, 62.6, 55.3, 53.3, 43.2, 42.3, 31.1, 27.3, 27.2. **IR:** 3017.0 (w), 2953.9 (w), 2927.3 (w), 2831.0 (w), 1737.2 (s), 1726.3 (s), 1712.0 (s), 1610.9 (m), 1452.8 (s), 1392.3 (m), 1365.0 (m), 1317.0 (m), 1245.5 (s), 1173.6 (s), 1028.3 (m), 931.4 (w), 831.0 (m), 747.6 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 441.0576, Obs. 441.0575.

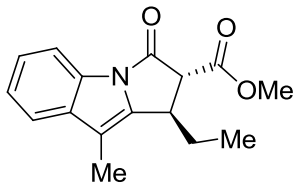


Methyl 9-(2-methoxy-2-oxoethyl)-1-(4-methoxyphenyl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-2-carboxylate (IV-36k): (*Z*)-Methyl 2-(3-(2-methoxy-2-oxoethyl)-1*H*-indole-1-carbonyl)-3-(4-methoxyphenyl)acrylate (0.075 g, 0.184 mmol), $In(OTf)_3$ (0.0103 g, 0.0184 mmol) and 1,2-DCE (5 mL) were combined according to the general procedure to afford **IV-36k** as a white solid (0.0698 g, 93%) after 3 h. R_f 0.40 (20% EtOAc/Hex). [**m.p.** 159-161 °C] *Diastereomeric ratio*: (13:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.12 – 8.05 (m, 1.07), 7.52 – 7.45 (m, 1.14), 7.39 – 7.29 (m, 2.27), 7.22 – 7.09 (m, 2.29), 6.92 – 6.80 (m, 2.25), 5.07 (d, *J* = 5.6 Hz, 1.10), 4.47 (d, *J* = 9.8 Hz, 0.08), 4.02 (d, *J* = 5.4 Hz, 1.00), 3.88 – 3.84 (m, 3.13), 3.81 – 3.77 (m, 3.40), 3.60 – 3.56 (m, 3.37), 3.47 – 3.38 (m, 1.11), 3.30 – 3.20 (m, 1.39). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.7, 167.7, 164.7, 159.3, 141.1, 135.1, 130.5, 130.1, 128.7, 124.7, 124.3, 119.1, 114.5, 114.0, 107.7, 62.6, 55.3, 53.2, 52.0, 42.2, 29.2. **IR**: 3046.9 (w), 3003.7 (w), 2957.2 (m), 2917.3 (w), 2824.4 (w), 1737.3 (s), 1725.9 (s), 1712.1 (s), 1608.9 (m), 1515.9 (m), 1453.0 (m),

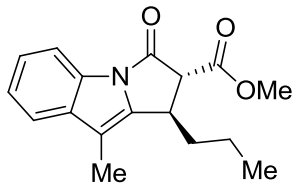
1349.8 (m), 1247.6 (m), 1158.9 (s), 1092.5 (m), 1031.8 (s), 951.3 (m), 835.4 (s), 753.9 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 407.1369, Obs. 407.1361.



Methyl 1-(4-methoxyphenyl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-2-carboxylate (IV-36l): (*Z*)-Methyl 2-(1*H*-indole-1-carbonyl)-3-(4-methoxyphenyl)acrylate (0.100 g, 0.298 mmol), $In(OTf)_3$ (0.0168 g, 0.0299 mmol) and DCE (5 mL) were combined according to the general procedure to afford **IV-36l** as a yellow solid (0.983 g, 98%) after 1 h. R_f 0.45 (30% EtOAc/Hex). *Diastereomeric ratio*: (10:1). [**m.p.** 113-115 °C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.12 – 8.05 (m, 0.95), 7.55 – 7.48 (m, 1.07), 7.38 – 7.27 (m, 2.24), 7.24 – 7.16 (m, 2.26), 6.92 – 6.81 (m, 2.24), 6.33 (dd, *J* = 1.7, 0.7 Hz, 0.10), 6.29 (dd, *J* = 1.7, 0.7 Hz, 0.96), 5.05 (dd, *J* = 5.6, 1.7 Hz, 1.09), 4.46 (d, *J* = 9.6 Hz, 0.10), 4.03 (d, *J* = 5.7 Hz, 0.98), 3.87 (s, 3.02), 3.81 (s, 3.00), 3.80 (s, 0.35), 3.26 (s, 0.27). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.0, 164.9, 159.3, 144.2, 135.3, 131.4, 130.5, 128.6, 124.7, 124.0, 121.0, 114.5, 114.0, 102.1, 77.2, 62.4, 55.3, 53.2, 42.5. **IR**: 3001.4 (w), 2927.7 (w), 2838.0 (w), 1730.2 (s), 1610.9 (m), 1589.6 (m), 1512.2 (m), 1474.9 (s), 1384.8 (m), 1322.0 (m), 1245.6 (s), 1162.0 (s), 1029.8 (m), 937.8 (w), 807.0 (s), 749.5 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 335.1158, Obs. 335.1158.

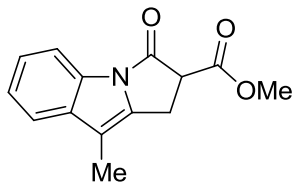


Methyl 1-ethyl-9-methyl-3-oxo-2,3-dihydro-1H-pyrrolo[1,2-*a*]indole-2-carboxylate (IV-36m): (*Z*)-Methyl 2-(3-methyl-1*H*-indole-1-carbonyl)pent-2-enoate (0.075 g, 0.276 mmol), $In(OTf)_3$ (0.0233 g, 0.0415 mmol) and toluene (4 mL) were combined according to the general procedure to afford **IV-36m** as a colorless oil (0.0665 g, 89%) after 14 h. R_f 0.50 (15% EtOAc/Hex). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.04 – 7.95 (m, 1H), 7.47 – 7.39 (m, 1H), 7.33 – 7.22 (m, 2H), 3.83 – 3.72 (m, 5H), 2.22 (s, 3H), 2.11 – 1.95 (m, 1H), 1.84 – 1.66 (m, 1H), 0.99 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.9, 165.2, 139.6, 136.5, 130.0, 124.2, 123.7, 118.7, 113.8, 109.7, 58.6, 53.0, 38.7, 26.5, 10.8, 8.5. **IR**: 3056.8 (w), 2963.8 (w), 2920.7 (w), 2867.5 (w), 1737.1 (s), 1725.2 (s), 1711.9 (s), 1635.4 (m), 1453.3 (m), 1396.6 (m), 1307.5 (m), 1250.9 (m), 1188.2 (w), 1027.4 (w), 948.0 (m), 745.4 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 271.1208, Obs. 271.1207.

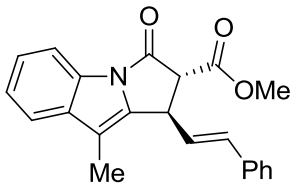


Methyl 9-methyl-3-oxo-1-propyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-2-carboxylate (IV-36n): (*Z*)-Methyl 2-(3-methyl-1*H*-indole-1-carbonyl)hex-2-enoate (0.075 g, 0.263 mmol), $In(OTf)_3$ (0.0221 g, 0.03945 mmol) and toluene (4 mL) were combined according to the general procedure to afford **IV-36n** as a colorless oil (0.0628 g, 84%) after 14 h (contaminated with ≤5% starting material as determined by ^{1}H NMR). R_f 0.30 (15%

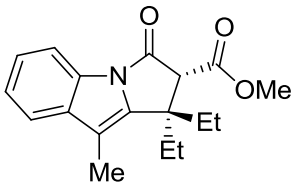
EtOAc/Hex). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.05 – 7.97 (m, 1H), 7.47 – 7.43 (m, 1H), 7.34 – 7.28 (m, 2H), 3.82 (s, 3H), 3.81 – 3.74 (m, 2H), 2.25 (d, *J* = 1.1 Hz, 3H), 2.04 – 1.90 (m, 1H), 1.77 – 1.65 (m, 1H), 1.43 (q, *J* = 15.4, 7.4 Hz, 2H), 0.99 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.0, 165.3, 140.0, 136.5, 130.1, 124.2, 123.7, 122.2, 118.7, 113.8, 109.6, 59.2, 53.1, 37.4, 36.0, 20.0, 13.9, 8.5. **IR**: 3073.4 (w), 2960.5 (m), 2924.0 (m), 2864.2 (m), 1737.0 (s), 1725.8 (s), 1712.5 (s), 1691.7 (s), 1630.3 (w), 1453.0 (s), 1435.7 (m), 1418.6 (m), 1396.0 (m), 1248.6 (m), 1212.6 (m), 1162.1 (m), 1059.1 (w), 1026.2 (w), 951.3 (w), 746.2 cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 285.1365, Obs. 285.1366.



Methyl 9-methyl-3-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-2-carboxylate(IV-36o): Methyl 2-(3-methyl-1*H*-indole-1-carbonyl)acrylate (0.100 g, 0.411 mmol), $In(OTf)_3$ (0.0355 g, 0.0632 mmol) and toluene (5 mL) were combined according to the general procedure to afford **IV-36o** as a pale yellow solid (0.0471 g, 47%) after 1 h. R_f 0.34 (20% EtOAc/Hex). [**m.p.** 95-97 °C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.04 – 7.97 (m, 1H), 7.49 – 7.41 (m, 1H), 7.35 – 7.27 (m, 2H), 4.15 (dd, *J* = 9.3, 4.9 Hz, 1H), 3.84 (s, 3H), 3.54 – 3.44 (m, 1H), 3.33 (ddd, *J* = 17.2, 9.3, 1.3 Hz, 1H), 2.20 (t, *J* = 1.3 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.8, 165.5, 136.4, 136.3, 130.4, 124.3, 123.6, 118.7, 113.8, 109.7, 53.2, 52.5, 23.0, 8.3. **IR**: **HRMS (ESI)** M/Z+ Calc. 243.0895, Obs. 243.

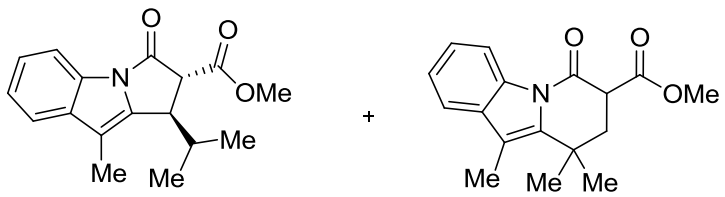


(*E*)-methyl 9-methyl-3-oxo-1-styryl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-2-carboxylate (IV-36p): (2*Z*,4*E*)-Methyl 2-(3-methyl-1*H*-indole-1-carbonyl)-5-phenylpenta-2,4-dienoate (0.0750 g, 0.209 mmol), $In(OTf)_3$ (0.0117 g, 0.0208 mmol) and 1,2-DCE (5 mL) were combined according to the general procedure to afford **IV-36p** as a pale yellow oil (0.0533 g, 71%) after 1 h. R_f 0.50 (15% EtOAc/Hex). *Diastereomeric ratio*: (8:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.11 – 8.01 (m, 1.14), 7.52 – 7.43 (m, 1.38), 7.42 – 7.26 (m, 8.52), 6.71 (d, *J* = 15.7 Hz, 1.14), 6.33 – 6.15 (m, 1.14), 4.64 (dd, *J* = 8.4, 5.1 Hz, 1.00), 4.55 (t, *J* = 9.2 Hz, 0.14), 4.39 (d, *J* = 9.5 Hz, 0.11), 3.97 (d, *J* = 5.0 Hz, 0.93), 3.87 (s, 3.03), 3.67 (s, 0.40), 2.20 (d, *J* = 1.3 Hz, 2.80), 2.18 (d, *J* = 1.2 Hz, 0.45). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.1, 164.4, 137.3, 136.4, 136.0, 133.2, 130.3, 128.7, 128.1, 126.5, 126.0, 124.4, 124.1, 119.0, 113.9, 111.5, 60.1, 53.2, 40.6, 8.2. **IR**: 3056.8 (w), 3033.6 (w), 2957.2 (w), 2917.3 (w), 2850.9 (w), 1738.4 (s), 1718.5 (s), 1715.1 (s), 1588.9 (w), 1446.1 (s), 1393.0 (s), 1363.1 (m), 1246.9 (s), 1160.5 (m), 964.6 (m), 745.4 (s), 692.2 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 345.1365, Obs. 345.1363.



Methyl 1,1-diethyl-9-methyl-3-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-2-carboxylate (IV-36q): Methyl 3-ethyl-2-(3-methyl-1*H*-indole-1-carbonyl)pent-2-enoate

(0.0800 g, 0.267mmol), $In(OTf)_3$ (0.0225 g, 0.0400 mmol) and toluene (4 mL) were combined according to the general procedure to afford **IV-36q** as a colorless oil (0.0784 g, 98%) after 12 h. R_f 0.40 (15% EtOAc/Hex). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.02 – 7.93 (m, 1H), 7.42 – 7.33 (m, 1H), 7.26 – 7.18 (m, 2H), 3.90 (s, 1H), 3.72 (s, 3H), 2.17 (d, *J* = 1.1 Hz, 3H), 2.06 – 1.64 (m, 4H), 0.90 – 0.73 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.0, 165.7, 140.8, 136.1, 129.9, 124.1, 123.8, 118.6, 113.9, 109.8, 104.9, 60.2, 52.4, 48.1, 29.9, 29.7, 9.1, 8.9. **IR:** 3036.9 (w), 2963.8 (m), 2934.0 (m), 2870.9 (m), 1748.3 (s), 1737.7 (s), 1725.2 (s), 1615.5 (w), 1453.6 (s), 1396.7 (s), 1303.3 (m), 1263.5 (m), 1158.6 (s), 1017.7 (m), 954.6 (w), 732.5 (s), 695.6 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 299.1521, Obs. 299.1521.

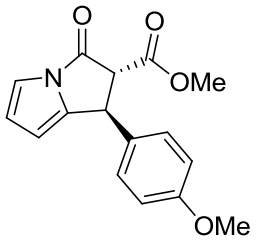


IV-36r **IV-37**

Methyl 1-isopropyl-9-methyl-3-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-2-carboxylate (IV-36r): (*Z*)-Methyl 4-methyl-2-(3-methyl-1*H*-indole-1-carbonyl)pent-2-enoate (0.075 g, 0.263 mmol), $In(OTf)_3$ (0.0148 g, 0.0263 mmol) and toluene (4 mL) were combined according to the general procedure to afford **IV-36r** as a white solid (0.063 g, 84%) after 12 h. R_f 0.40 (15% EtOAc/Hex). [**m.p.** 68-70 °C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.06 – 7.95 (m, 1H), 7.49 – 7.43 (m, 1H), 7.35 – 7.28 (m, 2H), 3.85 (d, *J* = 3.8 Hz, 1H), 3.82 – 3.77 (m, 4H), 2.39 (m, 1H), 2.25 (d, *J* = 1.0 Hz, 3H), 1.04 (d, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.3, 165.5, 139.3,

136.5, 130.1, 124.2, 123.7, 118.7, 113.8, 110.1, 55.0, 53.1, 43.8, 30.7, 20.2, 17.4, 8.8. **IR:** 3056.8 (w), 2947.2 (w), 2917.3 (w), 2864.2 (w), 1737.2 (s), 1725.3 (s), 1625.5 (w), 1453.2 (m), 1396.2 (m), 1307.9 (m), 1255.3 (m), 1161.6 (m), 1094.4 (m), 1031.0 (m), 954.6 (m), 805.2 (w), 745.7 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 285.1365, Obs. 285.1364.

Methyl 9,9,10-trimethyl-6-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indole-7-carboxylate (IV-37): Compound **IV-37** was afforded (0.00450 g, 6%) as a light brown oil (≥95% Purity!). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.48 – 8.42 (m, 1H), 7.47 – 7.41 (m, 1H), 7.35 – 7.28 (m, 2H), 3.94 – 3.83 (m, 4H), 2.59 – 2.45 (m, 1H), 2.34 (s, 3H), 1.98 (dd, *J* = 13.5, 4.9 Hz, 1H), 1.62 (s, 3H), 1.42 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.0, 165.3, 138.8, 134.1, 131.8, 124.9, 124.1, 117.7, 116.6, 113.2, 52.7, 48.1, 40.1, 32.0, 29.2, 26.8, 9.8. **IR:** 2955.7 (w), 2926.0 (w), 2870.0 (w), 1745.6 (s), 1696.5 (s), 1457.1 (s), 1394.6 (s), 1288.9 (w), 1196.6 (m), 1164.9 (m), 1123.2 (m), 1090.3 (m), 957.3 (w), 749.6 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 285.1365, Obs. 285.1369.



Methyl 1-(4-methoxyphenyl)-3-oxo-2,3-dihydro-1*H*-pyrrolizine-2-carboxylate (IV-39): (*Z*)-Methyl 3-(4-methoxyphenyl)-2-(1*H*-pyrrole-1-carbonyl)acrylate (0.152 g, 0.531 mmol), $In(OTf)_3$ (0.0308 g, 0.055 mmol) and 1,2-DCE (13 mL) were combined according to the general procedure to afford **IV-39** as a red oil (0.0817 g, 54%) after 12

h. R_f 0.35 (20% EtOAc/Hex). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.20 – 7.06 (m, 3.27), 6.91 – 6.78 (m, 2.20), 6.53 (t, *J* = 3.1 Hz, 0.10), 6.36 – 6.29 (m, 0.96), 6.02 – 6.00 (m, 0.08), 5.99 – 5.94 (m, 0.95), 4.87 (d, *J* = 3.9 Hz, 1.01), 4.40 (d, *J* = 9.1 Hz, 0.07), 3.92 (d, *J* = 5.1 Hz, 0.91), 3.85 (s, 2.96), 3.80 (s, 3.00), 3.79 (s, 0.67), 3.24 (s, 0.26). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.8, 165.5, 159.2, 140.5, 131.9, 128.4, 120.0, 114.4, 113.6, 111.7, 106.2, 105.0, 62.5, 55.3, 53.2, 42.4. **IR:** 3143.2 (w), 3106.6 (w), 3000.4 (w), 2957.2 (w), 2910.7 (w), 2837.6 (w), 1754.8 (s), 1737.3 (s), 1727.2 (s), 1608.9 (w), 1512.0 (m), 1401.6 (m), 1291.3 (m), 1242.7 (m), 1161.7 (m), 1080.8 (m), 974.5 (w), 901.5 (w), 833.4 (w), 719.4 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 285.1001, Obs. 285.1004.

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CHAPTER 5

INDIUM(III)- CATALYZED INTRAMOLECULAR FRIEDEL-CRAFTS APPROACH TO FUNCTIONALIZED PYRROLO[3,2,1-*ij*] QUINOLIN-4-ONES[††]

5.1. IMPORTANCE OF PYRROLO[3,2,1-*ij*]QUINOLINES

Heterocyclic compounds, especially nitrogen-containing heterocycles, are a prominent class of compounds in the pharmaceutical and agrochemical industries, with heterocycles constituting around 60% of all drug substances. Among heterocyclic compounds, tetrahydroquinoline (THQ) **V-1** is a common structural motif found in numerous biologically active natural products and pharmacologically relevant therapeutic agents.[1] Within the THQ class of compounds, the pyrrolo[3,2,1-*ij*]quinolines derivatives have garnered considerable attention in the area of drug discovery and agrochemistry due to its structural diversity (Figure 5.1).

[††]This work was performed in collaboration with Marchello A. Cavitt, a fellow graduate student and Paul Grzybowski, an undergraduate student in the France research group.

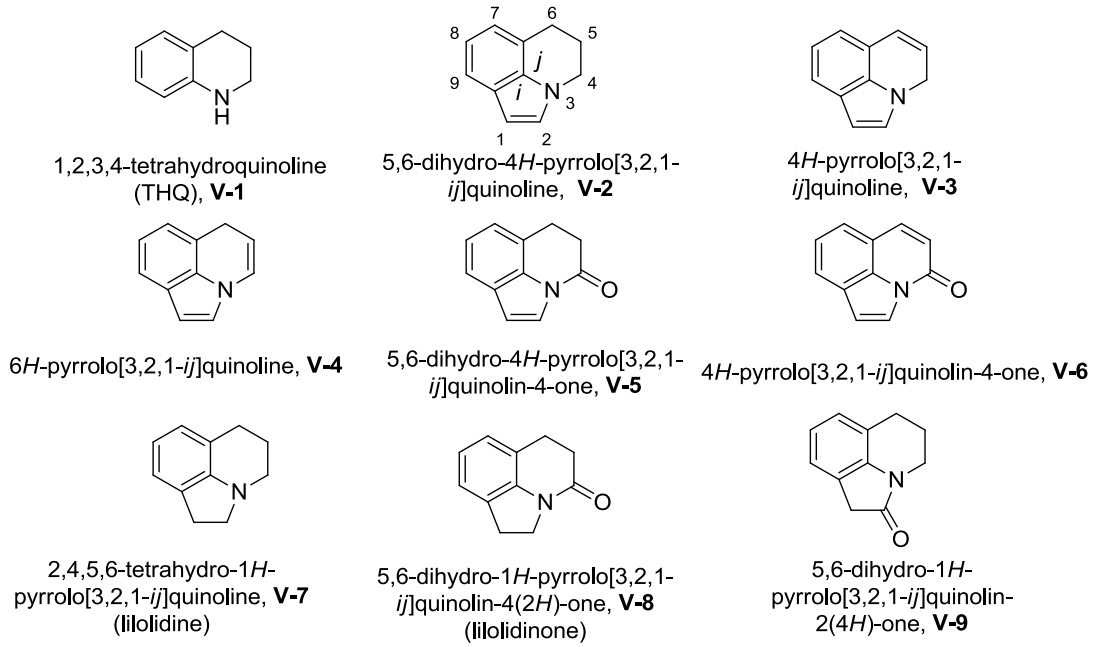


Figure 5.1. THQ Core and Representative Pyrrolo[3,2,1-*ij*]quinoline Frameworks

The pyrrolo[3,2,1-*ij*]quinolines are primarily characterized by two isomeric structures (4*H*-pyrrolo[3,2,1-*ij*]quinoline **V-3**, and the 6*H*-pyrrolo[3,2,1-*ij*]quinoline **V-4**) or by the reduced and oxidized forms **V-2**, and **V-5** to **V-9**. From among them, compounds containing a 4*H*-pyrrolo[3,2,1-*ij*]quinoline core have been found to exhibit interesting physiological and therapeutic properties (Figure 5.2). For example, the compound **V-10** acts as an antagonist for the human MT1 and MT2 melatonin receptor subtypes expressed in NIH 3T3 cells.[2] Derivative **V-11** possesses good anticonvulsant properties;[3] the compound **V-12** was identified as acetylcholinesterase inhibitor for the treatment of voiding dysfunction.[4] Quinoline derivative **V-13** were shown to have high activity towards *Mycobacterium* tuberculosis H37Rv (ATCC 27294) strain.[5] Compounds **V-14** act as an inhibitor of the enzyme farnesyl protein transferase (FPT).[6] The pyrroloquinoline derivative **V-15**, was identified as an inhibitor of aldosterone synthase

(CYP11 B2), a lead candidate for the treatment of hyperaldosteronism, congestive heart failure, and myocardial fibrosis.[7] Another compound, **V-16**, shows potent antagonistic property at 5-HT_{2A} in the potential treatment of psychosis.[8] PHA-529311 (**V-17**) shows inhibitory activity against herpesvirus DNA polymerases,[9] and derivative **V-18** acts as a potential SIRT1 activator (sirtuin 1) for the treatment of type II diabetes and other metabolic disorders.[10] KC11404 (**V-19)**, has been identified as a lead candidate for the potential treatment of asthma, demonstrated potent histamine and platelet activating factor (PAF) antagonism and 5-lipoxygenase inhibitory properties.[11] Another pyrrolo[3,2,1-*ij*]quinoline derivative **V-20** have been reported to be highly potent agonists at 5-HT_{2c} (5-hydroxytryptamine) with selectivity over 5-HT_{2a} isoform for the prophylactic management of epilepsy and obesity.[12] Recently, Turov *et al*. showed that the **V-21** derivative has high diuretic activity. The pyrrrolo[3,2,1-*ij*]quinoline derivatives were also found to be key intermediates towards the synthesis of other bioactive compounds.[13] Finally, the 1,2,5,6-tetrahydro-4*H*-pyrrrolo[3,2,1-*ij*]quinoline system is present at the core of the lilolidine (**V-7**) alkaloids,[14] which have been explored as therapeutics, fungicides (i.e., lilolidone **V-8**)[15] and as red-light-emitting dopants in organic light-emitting diodes (OLEDs) **V-22**. [16]

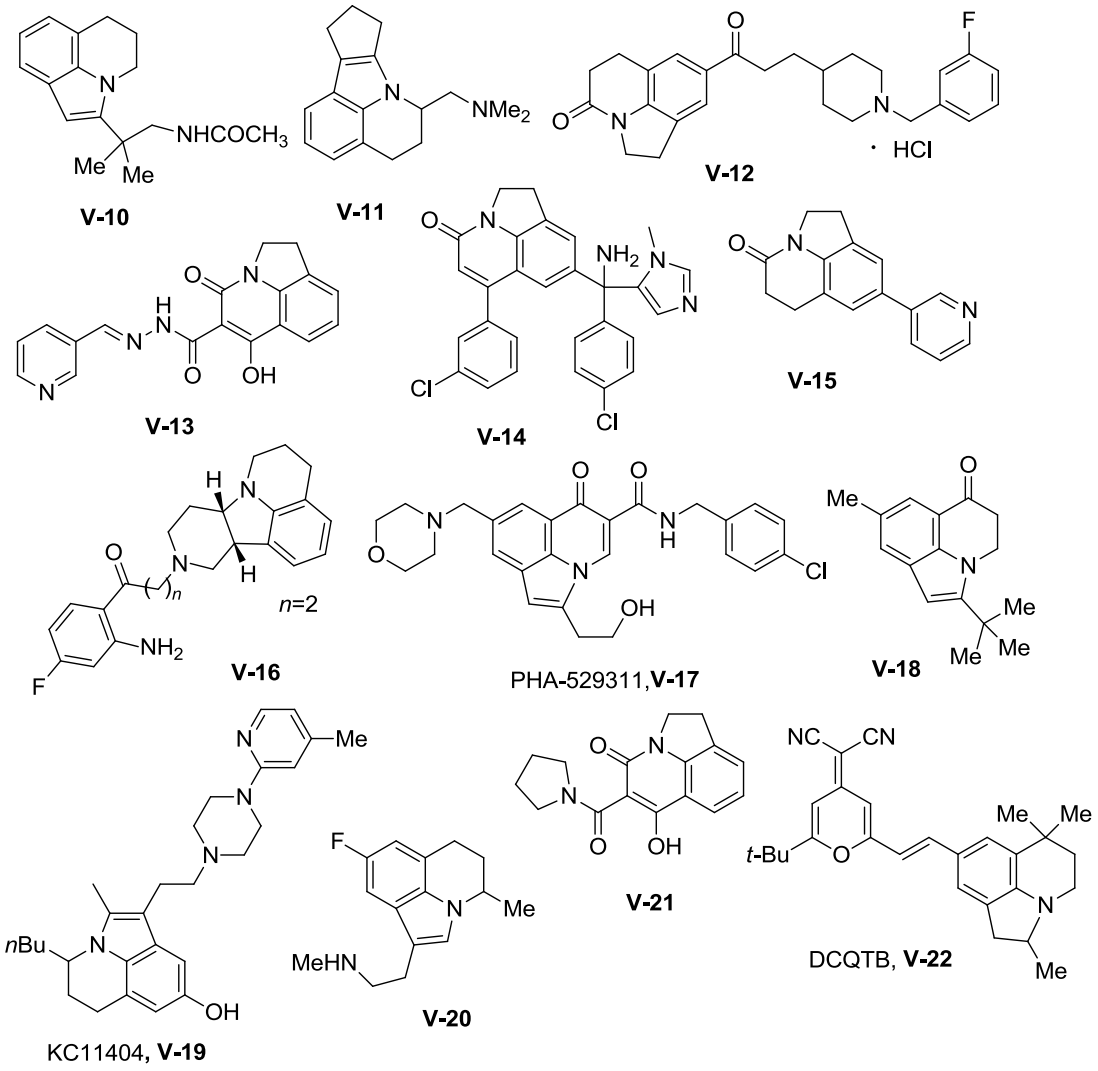


Figure 5.2. Examples of Pyrrolo[3,2,1-*ij*]quinoline Based Compounds

5.2. PREVIOUS METHODS FOR PYRROLO[3,2,1-*ij*] QUINOLINE SYNTHESIS

While a number of methods have been reported for the synthesis of pyrrolo[3,2,1-*ij*]quinoline (PQ) derivatives **V-2**, a majority of these strategies can be classified for clarity into two major categories: the construction of (i) six-membered ring using an indole template **B** or (ii) five-membered ring using a suitably substituted 1,2,3,4-tetrahydroquinoline **A** (Figure 5.3). The traditional, simple, and very popular synthetic

methods of PQs involve either Fischer indolization,[12,8,3,11] Friedel-Crafts-type substitution of the aromatic ring[7, 17] or transition-metal catalyzed annulations.[10, 18] Other less popular synthetic approaches are free radical cyclizations,[19] sigmatropic rearrangements,[20] the Pummerer reaction,[21] a Knoevenagel-type cyclization,[22] C-H functionalization,[23] base-mediated cyclizations,[24] benzotriazole methodology,[25] the Wittig reaction,[26] and the Michael–type annulation.[6, 15] In this section, the major synthetic methodology for the formation of such heterocycles will be reviewed with an example given for each synthetic route.

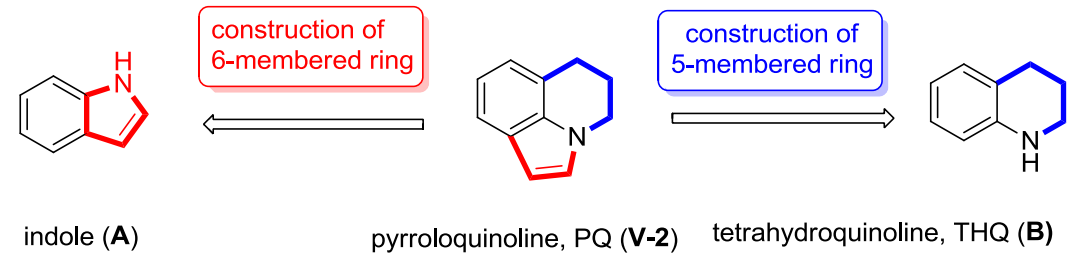


Figure 5.3. Pathways for the Synthesis of Pyrrolo[3,2,1-*ij*]quinolines

5.2.1. ROUTES FOR THE CONSTRUCTION OF FIVE MEMBERED RINGS

5.2.1.1. FISCHER INDOLIZATION REACTIONS

In 1983, the Stanton group reported Fischer indolization of 1-aminotetrahydroquinoline **V-23** with cyclopentanone in the presence of hot glacial acid afforded indole product **V-24** in 37% yield (Figure 5.4).[3]

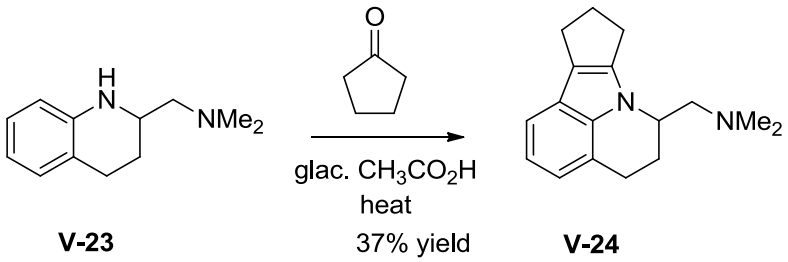


Figure 5.4. Fischer Indolization Reaction in the Synthesis of Pyrrolo[3,2,1-*ij*]quinolines

Jasserand and co-workers synthesized a series of compounds based on pyrrolo[3,2,1-*ij*]quinoline structures using the Fischer indole reaction.[11] The reaction of 1-amino-1,2,3,4-tetrahydroquinolines **V-25** with ethyl levulinate in the presence of HCl/AcOH at 80 ^{o}C, afforded **V-26** (Figure 5.5). These compounds were ultimately converted into **V-27**, which were tested for their pharmacological activities against three mediators associated with asthma-histamine, PAF, and leukotrienes.

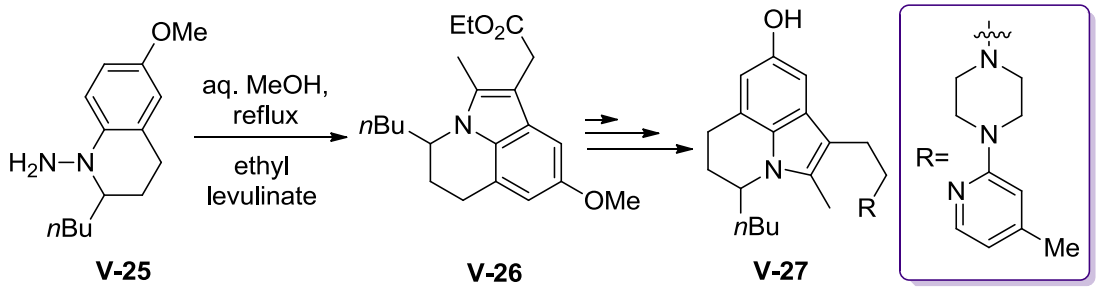


Figure 5.5. Synthesis of Pyrrolo[3,2,1-*ij*]quinolines via Fischer Indole Cyclization

The Isaac group synthesized pyrrolo[3,2,1-*ij*]quinolines derivatives using a Fischer indole cyclization route while developing an agonist at the 5-HT_{2c} receptor for the potential treatment of epilepsy and obesity.[12] The 1-amino-1,2,3,4-tetrahydroquinoline **V-28** was reacted with 4-chlorobutanal in aqueous methanol at reflux to afford desired product **V-29** in good yield. Resulting compound was transformed into *N*-methylated derivative **V-30** using Boc_2O followed by reduction with LAH (Figure

5.6). When tested, the compound **V-30** was found to be very potent at the 5-HT_{2c} (5-hydroxytryptamine) receptor with selectivity over the 5-HT_{2a} isoform.

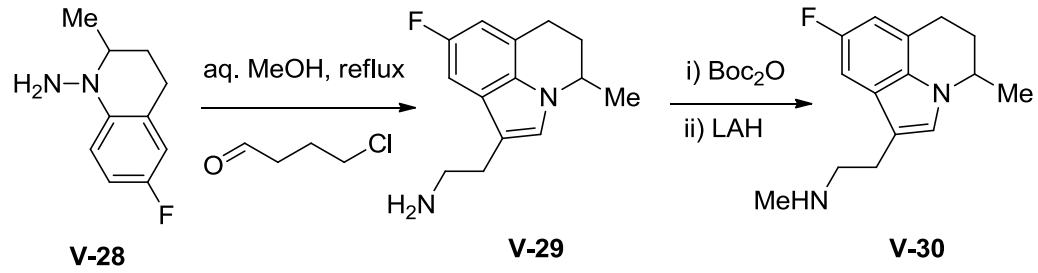


Figure 5.6. Fischer Indole Cyclization in the Synthesis of Pyrrolo[3,2,1-*ij*]quinolines

5.2.1.2. TRANSITION METAL-CATALYZED REACTIONS

In 2009, the Pal group developed a copper catalyzed C-N bond forming reaction towards the synthesis of 2-substituted pyrrolo[3,2,1-*ij*]quinolines.[18h] When 8-iodo-6-bromo-1,2,3,4-tetrahydroquinoline **V-31** was reacted with requisite alkynes in the presence of 10 mol% of Pd/C, furnished 8-alkynyl-1,2,3,4-tetrahydroquinolines **V-32.** Subsequent cyclization upon subjecting to 10 mol% CuI in DMF at 100 ^{o}C afforded pyrroloquinoline derivatives **V-33**. The reaction worked well for aryl and alkyl substituted alkynes, providing products in moderate to good yields. Pal also demonstrated the scope of this reaction by performing further structural elaboration via Pd-catalyzed coupling reaction to provide products **V-34** (Figure 5.7).

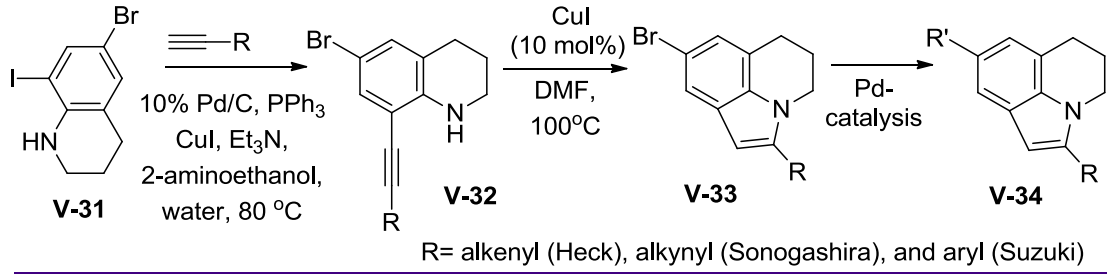


Figure 5.7. Copper Catalyzed Cyclization to Generate Pyrrolo[3,2,1-*ij*]quinolines

In continuation of the above studies, Pal and co-workers disclosed a two step, transition metal-catalyzed synthesis of 5-subsituted pyrrolo[3,2,1-*ij*]quinolines **V-36**.[10] The reaction sequence involved Sonogashira coupling of 6-substituted 8-iodo-2,3-dihydroquinolin-4(1*H*)-one **V-34** with requisite alkynes to generate 8-alkynyl-2,3-dihydroquinolin-4(1*H*)-one **V-35** followed by an intramolecular C-N bond formation reaction with 5 mol % $PdCl_2$ (Figure 5.8). Pal was also able to screen other substrates having EDG/EWG aryl, cyano, alkyl alcohol, alkyl halide, and alkyl substituents on the alkynes. The reactions proceeded smoothly in all cases with yields ranging from moderate to good. Further in their studies, easy derivatization of the resulting products was demonstrated by converting into chloro aldehydes and oxime derivatives. Finally, all the products were tested for potential SIRT1 activator towards the treatment of type II diabetes and other metabolic disorders.

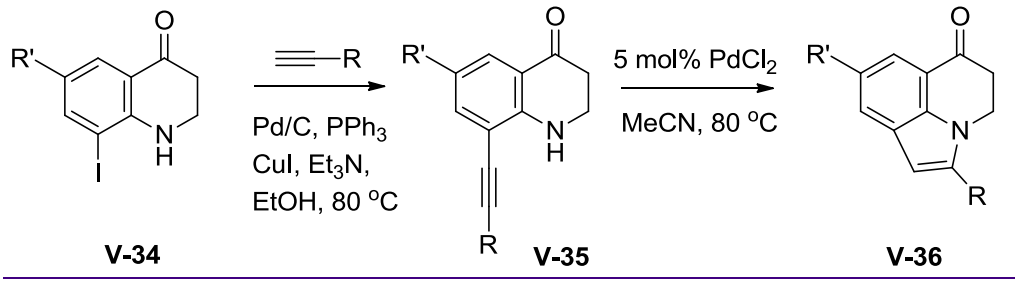


Figure 5.8. Palladium Catalysis in the Synthesis of Pyrrolo[3,2,1-*ij*]quinolines

Gunther *et al.* developed a novel Pd(II)-catalyzed intramolecular hetero-cyclization method for the synthesis of fused tricyclic quinolines **V-38** (Figure 5.9).[18i] The reaction involves $PdCl_2$-catalyzed heteroannulation of 6-bromo-8-(3,5-dimethylphenyl)ethynyl-1,2,3,4-tetrahydroquinolines **V-37**. Heteroannulation was

achieved in good yields. The reaction tolerates bromide, cyanide, and esters substituents on the THQ.

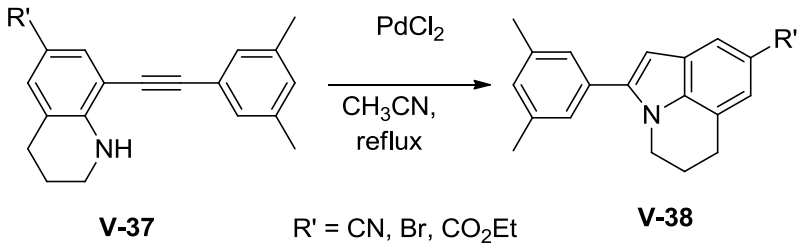


Figure 5.9. Pd(II)-Catalyzed Heteroannulation in Pyrrolo[3,2,1-*ij*]quinolines Synthesis

Recently, Liu and co-workers reported palladium-catalyzed oxidative aryltrifluoromethylation of activated alkenes.[18c] In one representative example, alkene **V-39** reacted with $TMSCF_3$/CsF in the presence of $Pd(OAc)_2$/$Yb(OTf)_3$ as a catalyst to generate pyrroloquinolines **V-40** (Figure 5.10). The reaction utilizes $TMSCF_3$/CsF as trifluoromethyl group source and $PhI(OAc)_2$ as oxidant.

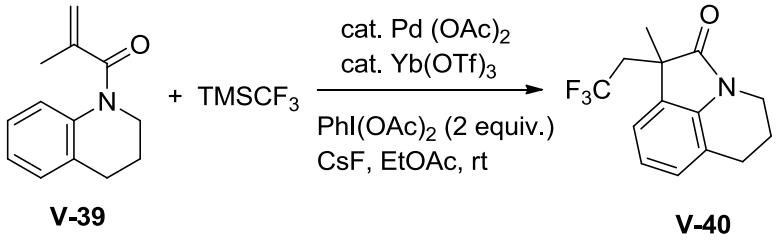


Figure 5.10. Pd(II)-Catalyzed Oxidative Aryltrifluoromethylation of Activated Alkenes

Wipf and group disclosed titanocene(III)-catalyzed reductive cyclization of an epoxide tethered to substituted anilines and aminopyridines to form indoles and azaindolines.[18f] For example, *N*-tetrahydroquinoline substituted epoxide **V-41**

titanocene(III) chloride-catalyzed ring-opening of epoxide followed by arene annulation to provide pyrroloquinolines **V-42** in good yield (Figure 5.11).

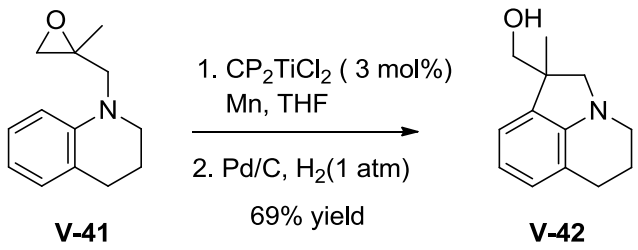


Figure 5.11. Titanocene(III)-Catalyzed Synthesis of Pyrrolo[3,2,1-*ij*]quinolines

In 2010, the Zhu group developed Pd(II)-catalyzed carbo-heterofunctionalization of activated alkenes for the synthesis of oxindoles and spirooxindoles.[18e] In one example, *N*-tetrahydroquinoline substituted alkene **V-43** successfully cyclized in the presence of $Pd(OAc)_2/PhI(OAc)_2$ at 100 ^oC in acetic acid to generate iodo-substituted pyrroloquinoline product **V-44** (Figure 5.12). Along this line, Zhu also reported iodo-carbocylization of electron deficient alkenes towards the synthesis of oxindoles and spirooxindoles.[27]

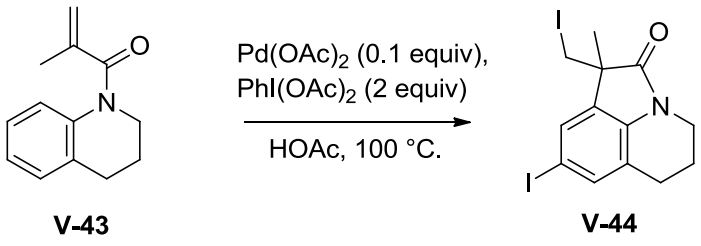


Figure 5.12. $Pd(OAc)_2$-Catalyzed Carbo- Heterofunctionalization to Generate PQ's

5.2.1.3. SIGMATROPIC REARRANGEMENT REACTIONS

In 1989, the Majumdar group developed a straight-forward one-pot reaction for the synthesis of substituted pyrrolo[3,2,1-*ij*]quinolines.[20a] Treatment of 1-aryloxy-4-tetrahydro-l-quinoylbut-2-ynes **V-45** with *m*CPBA at room temperature for 12 h, facilitated a spontaneous [2,3]-followed by [3,3]-sigmatropic rearrangement to provide unstable aminol intermediate **V-46**. Addition of a stronger nucleophile such as KCN, provided the title compounds **V-47** in 55-75% yield (Figure 5.13).

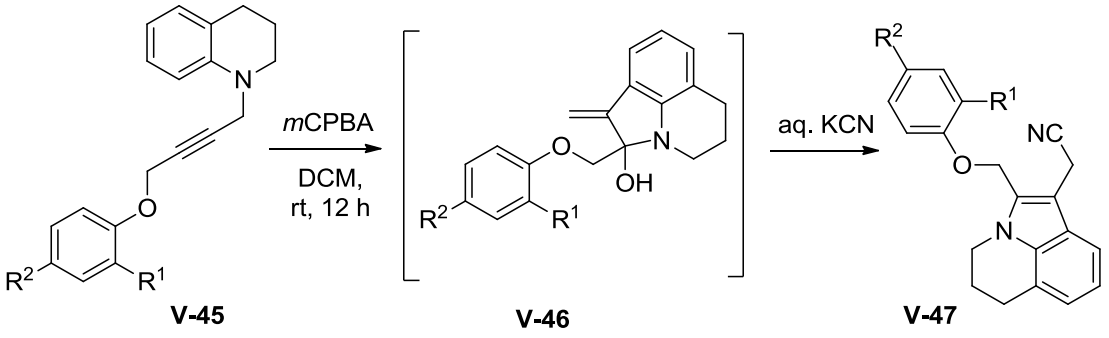


Figure 5.13. Sigmatropic Rearrangement in the Synthesis of Pyrrolo[3,2,1-*ij*]quinolines

In an analogous fashion to amine oxides above, the [2,3]-sigmatropic rearrangement reaction of azasulphenium ylides has also been used in the construction of pyrrolo[3,2,1-*ij*]quinoline ring systems (Figure 5.14). In 1984, the Gassman group reported one-step synthesis of pyrrolo[3,2,1-*ij*]quinolines.[20b] When 1,2,3,4-tetrahydroquinoline **V-48** was reacted with chlorosulfonium chloride **B** followed by treatment with Et_3N, product **V-49** was furnished in 53% yield. Furthermore, reaction of **V-48** with chlorosulfonium chloride salt **B** furnished product **V-50** in 39% yield (Figure 5.14).

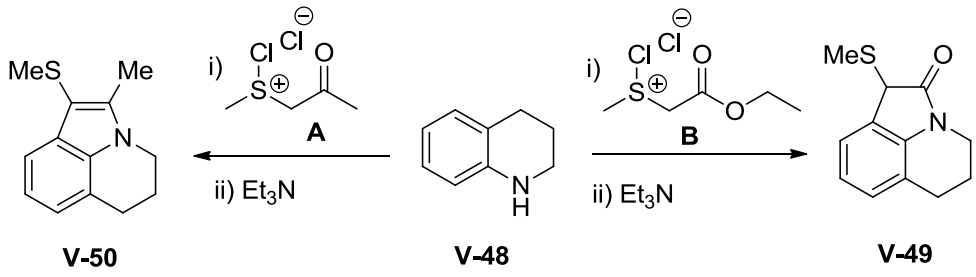


Figure 5.14. [2,3]-Sigmatropic Rearrangement of Azasulephenium Ylides

5.2.1.4. BASE MEDIATED CYCLIZATION REACTIONS

Guiotto and co-workers used a base mediated cyclization strategy to synthesize pyrrolo[3,2,1-*ij*]quinolines.[24] The reaction of 8-(dibromopropyl)quinoline-2-one derivatives **V-51** with 5% aq. KOH in ethanol at reflux, unexpectedly afforded only desired products **V-52** in about 43-55 % yield (Figure 5.15).

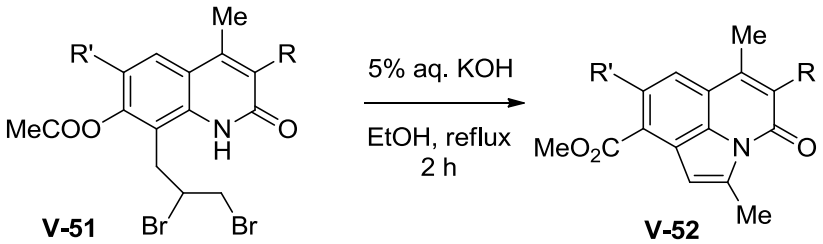


Figure 5.15. Base Mediated Synthesis of Pyrrolo[3,2,1-*ij*]quinolines

5.2.1.5. PUMMERER CYCLIZATION REACTION

Proctor and co-workers disclosed a fluorous-phase Pummerer cyclative-capture strategy for the synthesis of pyrroloquinolines.[21a] The addition of thiols to glyoxamides **V-53** in the presence of trifluoroacetic anhydride formed hemithioacetals, which upon subsequent activation by $BF_3.Et_2O$ underwent Pummerer cyclization to afford product **V-54** in 65% yield (Figure 5.16).

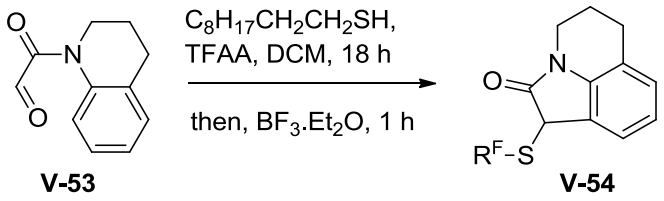


Figure 5.16. Pummmerer Reaction in the Synthesis of Pyrrolo[3,2,1-*ij*]quinolines

5.2.1.6. C-H ACTIVATION REACTIONS

Recently, the Yang group developed a silver-catalyzed intramolecular cyclization via C-H activation to generate 1-alkylidene substituted pyrroloquinoline.[23a] The reaction of diazoamide **V-55** in the presence of 5 mol% AgOTf as the catalyst in dioxane at 100^{o}C, furnished with 61% of the desired quinoline derivatives **V-56** (Figure 5.17).

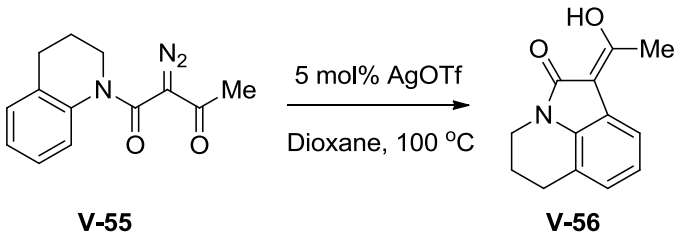


Figure 5.17. Synthesis of Pyrrolo[3,2,1-*ij*]quinolines via C-H Activation

5.2.2. ROUTES FOR THE CONSTRUCTION OF SIX MEMBERED RINGS

5.2.2.1. FRIEDEL-CRAFTS CYCLIZATION REACTION

In 2011, the Hartmann group reported the synthesis of heteroaryl substituted 1,2,5,6-tetrahydropyrrolo[3,2,1-*ij*]quinolin-4-one derivatives.[7] Indoline **V-57** was first converted into amide followed by a FC-cyclization to afford pyrrolo[3,2,1-*ij*]quinolines **V-58**. These fused heterocycles were then regioselectively brominated by treating with NBS in DMF at 0 ^{o}C. Finally, arylbromide were subjected to Suzuki coupling with an *N*-

heterocyclic boronic acid to provide heteroaryl substituted products **V-59** (Figure 5.18). Furthermore, these derivatives were tested for inhibition of aldosterone synthase (CYP11 B2), a promising target for the treatment of hyperaldosteronism, congestive heart failure, and myocardial fibrosis. Interestingly, derivatives of **V-59** were found to be more potent and selective CYP11B2 inhibitors than their parent analogues.

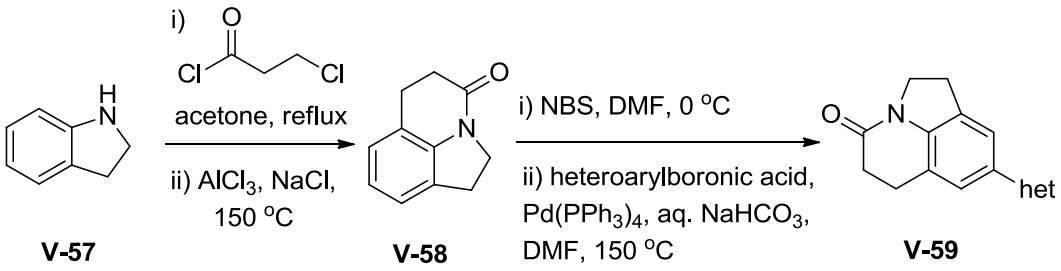


Figure 5.18. Synthesis of Heteroaryl Substituted PQ's via F-C Reaction

5.2.2.2. MICHAEL-TYPE CYCLIZATION REACTION

In the works of Angibaud and co-workers,[6] pyrrolo[3,2,1-*ij*]quinoline intermediate **V-60** was generated by acylation of indoline **V-57** with 3-chlorocinnamoyl chloride followed by PPA-catalyzed F-C acylation. The resulting tetrahydroquinolines were ultimately used in the preparation of **V-61** (Figure 5.19). Further studies showed that compound **V-61** has inhibitory activity for the enzyme farnesyl protein transferase (FPT). Inhibition of FPT would prevent a key step in the post-translational processing of *Ras* and the subsequent propagation of cell growth promoting signals. This would have potential application as anticancer agents for tumors in which *Ras* contributes.

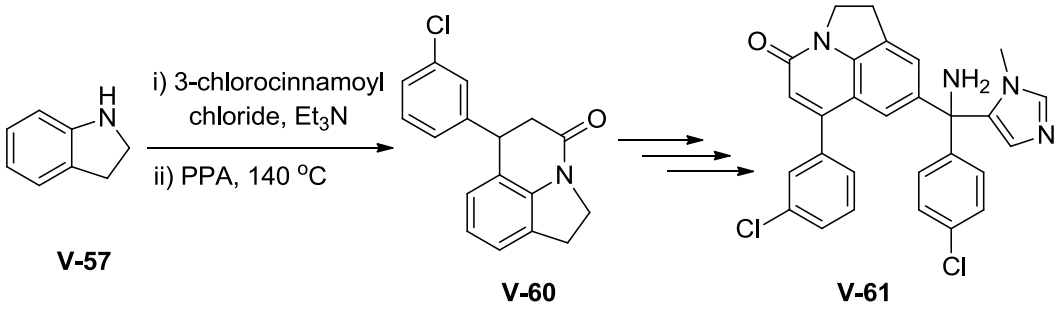


Figure 5.19. Synthesis of Pyrrolo[3,2,1-*ij*]quinolines by Michael-Type Reaction

5.2.2.3. SIGMATROPIC REARRANGEMENT REACTION

Lingam *et al.* reported a simple and novel synthesis of pyrrolo[3,2,1-*ij*]quinoline derivatives **V-63** by the polyphosphoric acid (PPA)-catalyzed aza-Cope rearrangement reaction of 3-arylprop-2-en-1-yl amines **V-62** (Figure 5.20).[20c]

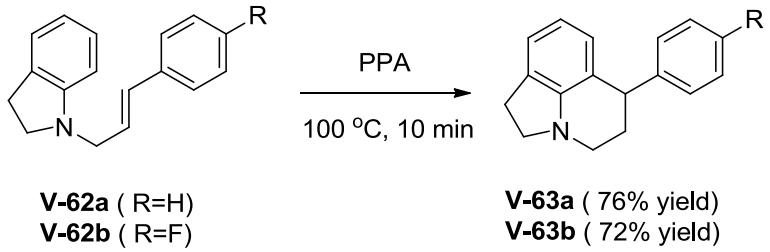


Figure 5.20. Pyrrolo[3,2,1-*ij*]quinoline Synthesis via Aza-Cope Rearrangement Reaction

5.2.2.4. TRANSITION METAL-CATALYZED REACTIONS

Chen and co-workers developed a chemoselective asymmetric *N*-allylic alkylation of indoles with Morita-Baylis-Hillman carbonates to deliver chiral indole derivatives **V-64**.[18a] Further in their studies, these precursors were subjected to intramolecular radical cyclization or Heck coupling to afford pyrrolo[3,2,1-*ij*]quinoline derivatives **V-65** in good yields and good enantioselectivity (Figure 5.21).

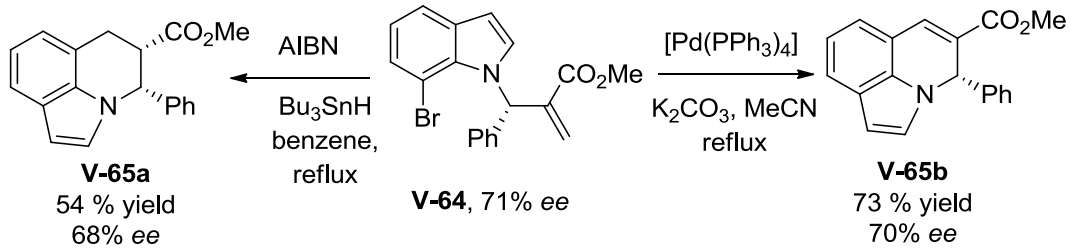


Figure 5.21. Pyrrolo[3,2,1-*ij*]quinolines by Radical Cyclization or Heck Coupling

The palladium-mediated *6-endo-trig* intramolecular Heck cyclization of *N*-acryloyl-7-bromoindolines **V-66** was developed by Dankwardt and co-workers in 1995 to generate tricyclic fused quinolines **V-67** in 88-99% yields (Figure 5.22).[18d] The reaction was proposed to go through a *6-endo* pathway presumably due to strain involved in the approach of the palladium species to the *α*-position of the double bond of these acrylamides, thus generally disfavoring the *5-exo-trig* mode of closure.

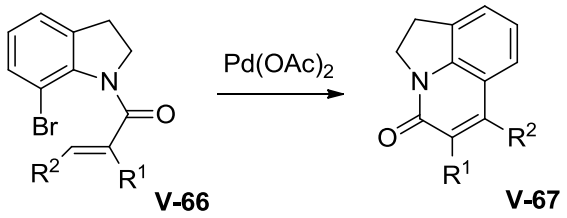


Figure 5.22. Pyrrolo[3,2,1-*ij*]quinolines by Intramolecular Heck Coupling Reaction

The palladium(II)-catalyzed cyclization of *N*-allyl-7-bromoindoles **V-68** to produce pyrroloquinoline derivatives **V-69** was reported by Black and co-workers in 1992 (Figure 5.23).[18g]

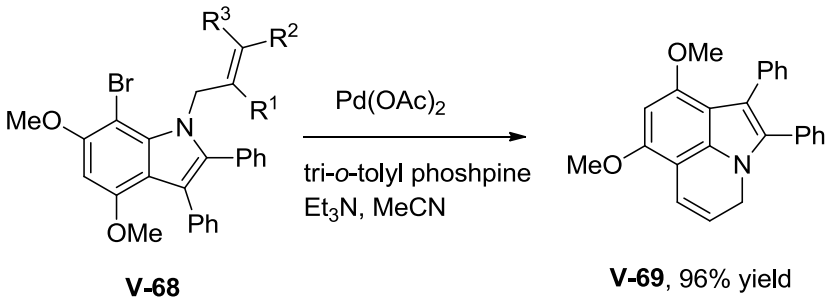


Figure 5.23. Heck Coupling Reaction in the Synthesis of Pyrrolo[3,2,1-*ij*]quinolines

In 2007 Alper *et al.* reported Rh(I)-catalyzed hydroaminomethylation strategy for the synthesis of quinolines. The 2-isopropenylindolines **V-70** was reacted with 5.0 mol% Rh(I) at 120 ^{o}C in toluene under 1000 *psi* CO/H_2 for 48 h to afford the title compound **V-71** (Figure 5.24).[18b]

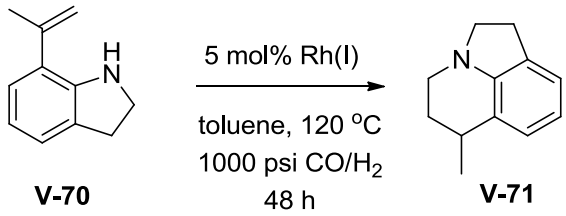


Figure 5.24. Rh(I)-Catalyzed Hydroaminomethylation Reaction

5.2.2.5. INTRAMOLECULAR WITTIG REACTION

In 2006, Adib and co-workers reported a one-pot synthesis of 4*H*-pyrrolo[3,2,1-*ij*]quinolines using an intramolecular Wittig reaction.[26] When acetylenic esters **V-72** were reacted with indole-7-carboxaldehyde **V-73** in the presence of triphenylphosphine product **V-74** was formed in quantitative yield (Figure 5.25).

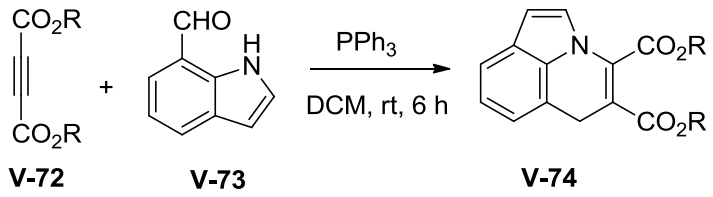


Figure 5.25. Synthesis of Pyrrolo[3,2,1-*ij*]quinolines via Wittig Reaction

5.2.2.6. FREE RADICAL CYCLIZATION/PHOTOCYCLIZATION

The Padwa group has employed radical cyclization for the synthesis of the octahydropyrrolo[3,2,1-*ij*]quinoline ring system.[19c] The reaction of *N*-allyl-7-bromo-3a-methylhexahydroindolinone **V-75** with *n*-Bu_3SnH/AIBN in benzene at reflux provided the desired tricyclic product **V-76** in 89% yield (Figure 5.26).

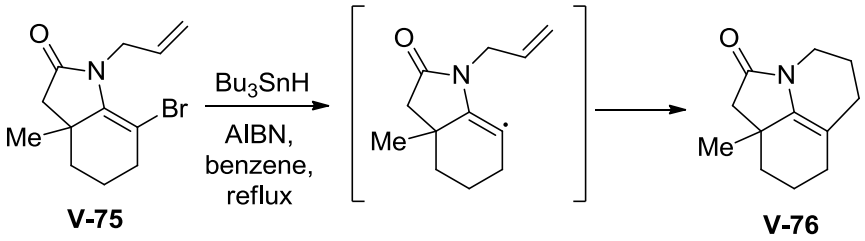


Figure 5.26. Octahydropyrrolo[3,2,1-*ij*]quinolines by Radical Cyclization Reaction

West and co-workers reported intramolecular radical cyclization reaction involving *ipso*-substitution using sulfone substituted indoles. When 7-sulfone substituted indolines **V-77** reacted in the presence of Bu_3SnH/AIBN in toluene at reflux pyrroloquinolines **V-78** was formed in 57% yield (Figure 5.27).[19b]

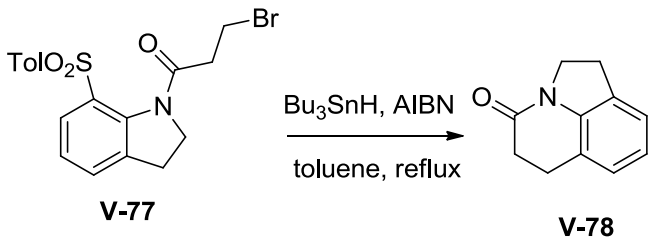


Figure 5.27. Pyrrolo[3,2,1-*ij*]quinolines by Intramolecular Radical Cyclization Reaction

5.2.2.7. C-H ACTIVATION REACTIONS

In 2005, Yi and co-workers generated pyrroloquinolines using ruthenium-catalyzed regioselective hydroamination and C-H bond activation reaction.[23b] As shown in Figure 6.28, substituted indolines **V-79** on treatment with large excess of alkynes in the presence of $Ru_3(CO)_3/NH_4PF_6$ (1:3) in benzene at reflux for 12-26 h cleanly produced tricyclic quinoline products **V-80** in 42-99 % yields. The alkyl, aryl, halogen and alkylether groups are well tolerated in the reaction. The reaction is postulated to proceed via ruthenium-mediated *ortho*- C-H bond insertion of an alkyne to form the *ortho*-vinylated amine, the hydroamination of the second alkyne, and the subsequent electrocyclization to give the product **V-80**.

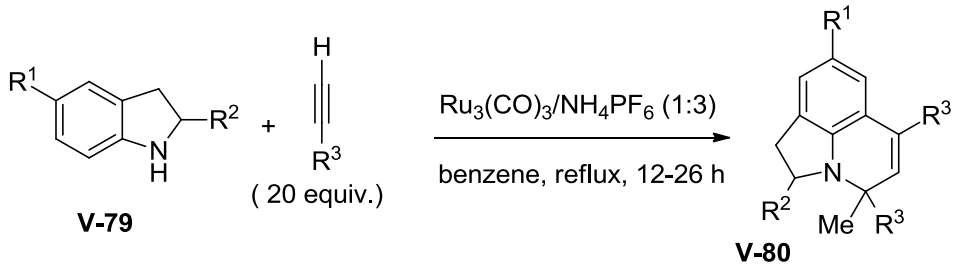


Figure 5.28. Ruthenium-Catalyzed Hydroamination and C-H Activation Reaction

5.2.2.8. BENZOTRIAZOLE METHODOLOGIES

In 2001, Abonia and co-workers disclosed benzotriazole methodology towards the synthesis of pyrroloquinolines.[25b] Under acidic conditions (*p*-TsOH), the benzotriazolyl-derivatives of indolines **V-81** were transformed to products **V-82** in good yields on reaction with terminal alkenes (Figure 5.29). Abonia also demonstrated that 1-vinyl-2-pyrrolidinone, dihydrofuran, dihydropyran, alkyl vinyl ethers, and styrenes can act as a suitable alkene partners.

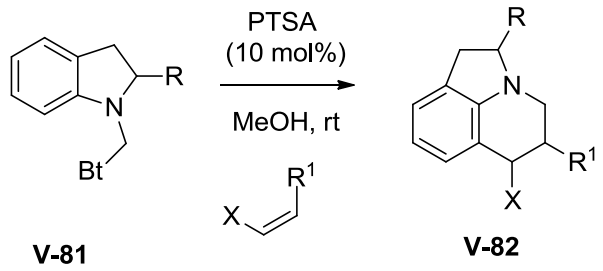


Figure 5.29. Benzotriazole Methodology in the Synthesis of Pyrrolo[3,2,1-*ij*]quinolines

5.2.2.9. KNOEVENAGEL REACTION

In 2004, Zhu and co-workers reported the synthesis of 1,7-annulated indoles during their study directed towards the development of cyclin kinase dependent inhibitors.[22] The 7-formylindole was *N*-alkylated with 3-bromopropionate, which subsequently underwent Knoevenagel condensation in the presence of cesium carbonate provided quinoline product **V-83** (Figure 5.30).

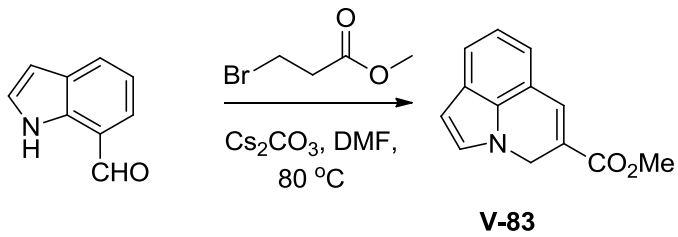


Figure 5.30. Synthesis of Pyrrolo[3,2,1-*ij*]quinolines via Knoevenegal Cyclization

5.2.2.10. MISCELLANEOUS APPROACHES

Kouznetsov *et al.* employed a H_2SO_4-induced FC-alkylation reaction to generate 4*H*-spiro[pyrrolo-[3,2,1-*ij*]quinolines. Upon heating the *N*-allyl substituted amine **V-84** at 90°C with 85% H_2SO_4, afforded desired product **V-85** via *N*-allyl spiroquinoline intermediate **A** (Figure 5.31).[17e]

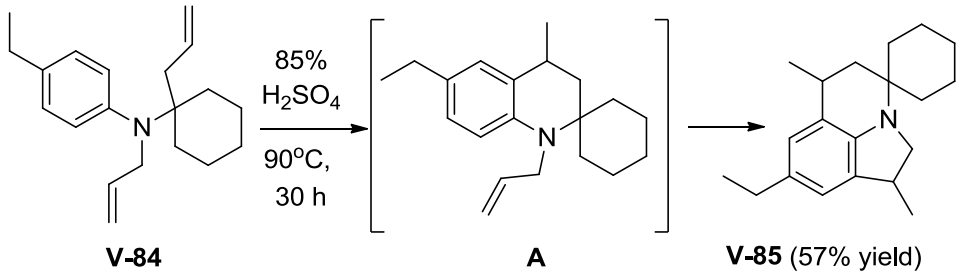


Figure 5.31. Spiropyrrolo[3,2,1-*ij*]quinolines via Double F-C Alkylation Reaction

In 2011, Zhang group have developed an efficient one-pot synthesis of benzo[*f*]pyrrolo[3,2,1-*ij*]quinolin-3-ones via photoannulation.[19d] The 6-chloropyridin-2-ones reacted with a tethered styrene **V-86** under photoreaction conditions in the presence of oxygen to afford products **V-87** in 50-56% yield (Figure 5.32). It was observed that EDG-groups on styrene retarded the photoreaction where as EWG-group accelerated the reaction. The reaction tolerates halogens, nitrile, ethers, and alkyl groups.

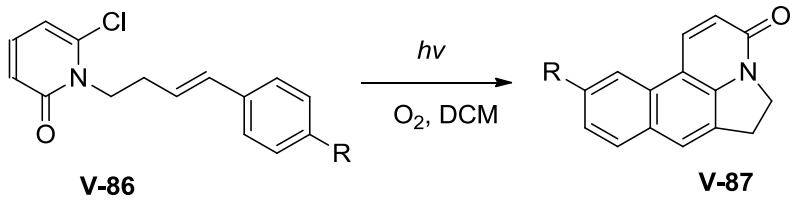


Figure 5.32. Double F-C Alkylation in the Synthesis of Spiropyrrolo[3,2,1-*ij*]quinolines

Katritzky and co-workers reported TsOH-catalyzed Friedel-Crafts-type ring closure of 5,6,7,8-tetrahydroindolizine derivative **V-89** to generate pyrrolo[3,2,1-*ij*]quinolines **V-90** in 65% yield.[25a] The required precursors were fashioned from tetrahydroindolizines **V-88** upon subjection to lithiation followed by a reaction with *trans*-chalcone (Figure 5.33).

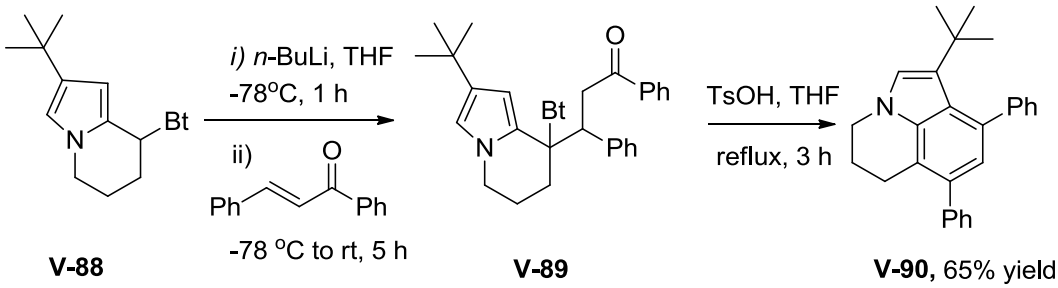


Figure 5.33. Pyrrolo[3,2,1-*ij*]quinolines via Benzotriazole Methdology

Aniline **V-91**, bearing both *N*-crotonyl and *N*-allyl groups was transformed to *N*-crotonyl indoline **V-92** through radical cyclization, which was subsequently subjected to silicon/iodine exchange reaction with ICl. The resulting iodide intermediate was reacted under similar radical cyclization conditions to provide the pyrroloquinoline products **V-93** (Figure 5.34).[19e]

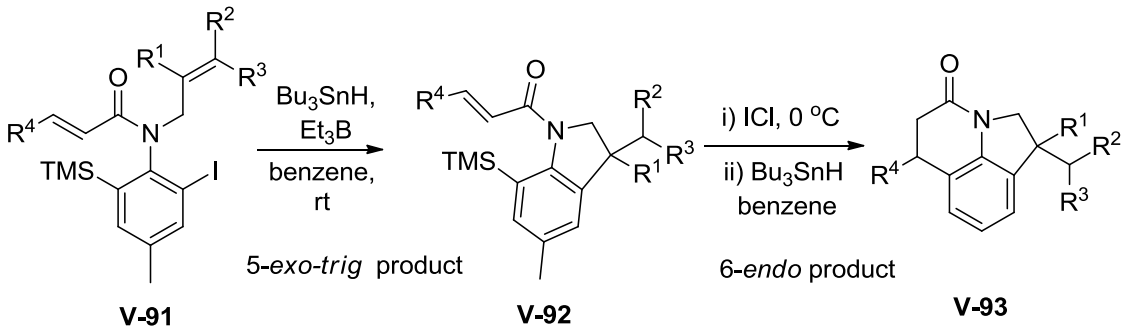


Figure 5.34. Double Radical Cyclization Approach to Pyrrolo[3,2,1-*ij*]quinolines

All of these methods have some good advantages but also have several drawbacks, such as long reaction times, tedious workup procedures, and occurrence of several side reaction products, lower yields, lack of generality of the reaction, use of harsh conditions, poor selectivity, and the use of expensive transition metals. Therefore, the search continues for a better and convenient method for the synthesis of pyrrolo[3,2,1-*ij*]quinolines derivatives in terms of operational simplicity, economic viability, and greater selectivity.

5.3. INDIUM(III)-CATALYZED INTRAMOLECULAR FRIEDEL-CRAFTS CYCLIZATION TO THE SYNTHESIS OF PYRROLO[3,2,1-*ij*]QUINOLINES

Previous work done in the France lab has demonstrated that $In(OTf)_3$ catalyzes intramolecular F-C alkylation of methyl 2-(1*H*-indole-1-carbonyl)acrylates **V-94** (Figure 5.35).[28] This method provided an efficient and diastereoselective route to the synthesis of functionalized 1*H*-pyrrolo[1,2-*a*]-indole derivatives **V-95**. In an extension of this methodology, the France lab envisioned that a similar intramolecular F-C reaction should occur by employing a substrate with the indole 2-position blocked, as in the methyl 2-(2-methyl-1*H*-indolecarbonyl) acrylate. With the 2-position unavailable, the only site for electrophilic attack would be the indole 7-position. Thus, cyclization would provide rapid access to pyrrolo[3,2,1-*ij*]quinolines compounds **V-96**. In recognizing the utility of this transformation, the France group sought to develop an annulation of *N*-substituted indolyl acrylates to access substituted pyrrolo[3,2,1-*ij*]quinolin-4-ones derivatives.

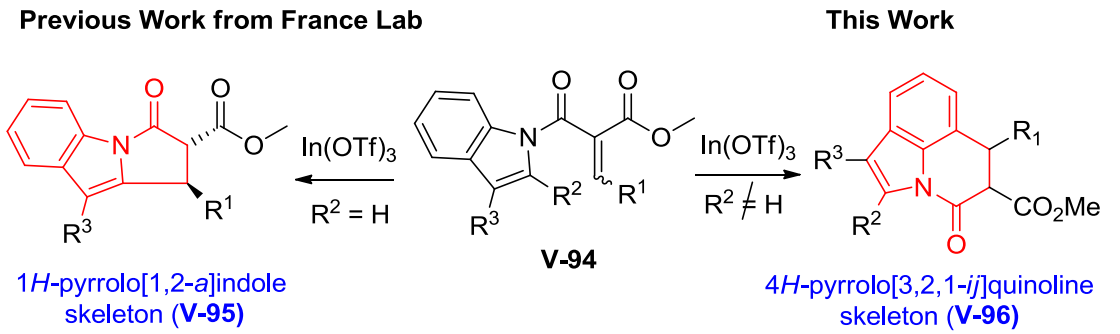


Figure 5.35. Proposed F-C Cyclization for the Synthesis of Pyrrolo[3,2,1-*ij*]quinolines

5.3.1. SUBSTRATE SYNTHESIS

To test this concept, the synthesis of the requisite acrylates was carried out as previously described.[28] The synthesis involved two-step reaction protocol, starting from commercially available indoles. First, treatment of indoles with methyl malonyl chloride afforded β-amidoesters. The required benzylidene malonate precursors **V-94** were then prepared from the corresponding aldehydes and β-amidoesters under Knoevenagel condensation conditions.

5.3.2. PROOF OF CONCEPT

The acrylate **V-94a** (derived from 2-methyl indole and *p*-anisaldehyde) was chosen for preliminary investigation, the decision was influenced from previous work of France and co-workers on the pyrrolo[1,2-*a*]-indoles **V-95.**[28] Initial efforts in the France group involved the examination of Lewis acids to achieve the desired F-C alkylation. We began by subjecting acrylate **V-94a** to 15 mol% $In(OTf)_3$ in toluene at reflux, a previously optimized condition used for the synthesis of pyrrolo[1,2-*a*]indoles **V-95**. As anticipated, **V-94a** readily cyclized to generate the desired pyrrolo[3,2,1-*ij*]quinoline product **V-96a** in 63% yield with 50:1 *trans*:*cis dr* (Figure 5.36, Table 5.1, entry 1).

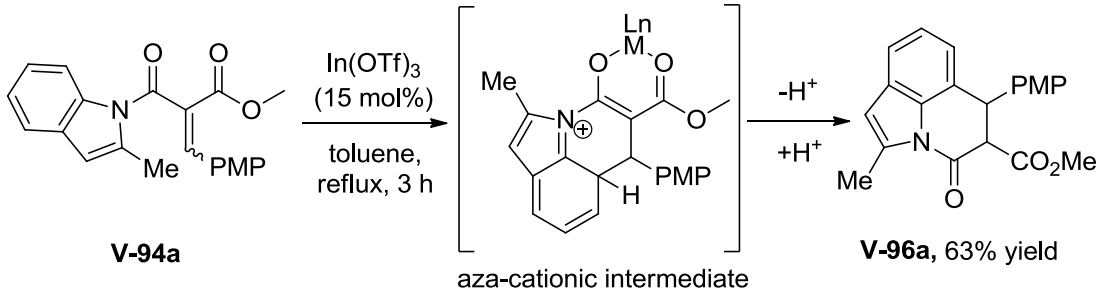
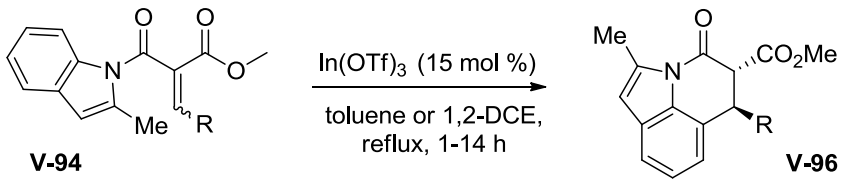


Figure 5.36. Test Reaction Towards the Synthesis of Pyrrolo[3,2,1-*ij*]quinolines

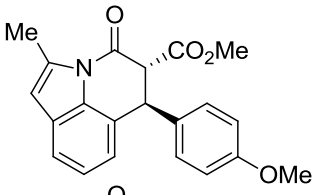
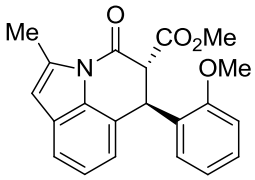
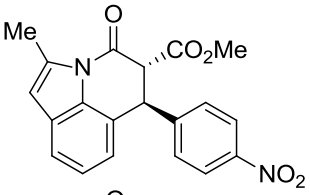
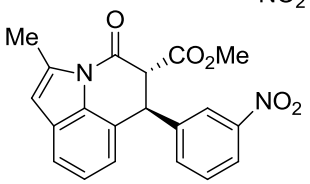
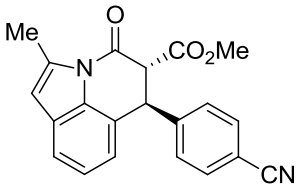
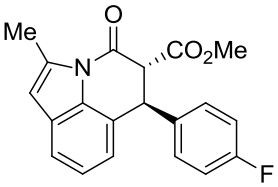
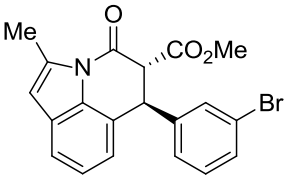
5.3.3. REACTION SCOPE STUDIES

With preliminary results in hand, subsequent studies sought to examine the scope and limitations of the In(III)-catalyzed intramolecular Friedel-Crafts alkylation of methyl 2-(2-methyl-1*H*-indole-1-carbonyl)acrylates. Early reaction development was carried out using acrylates **V-94** bearing substituted aryl group on alkene. Acrylate bearing an electron donating *o*-methoxy substituted phenyl **V-94b** readily cyclized to give its product **V-96b** in 87% yield (Table 5.1, entry 2), a reduced *dr* was observed (3.7:1). We primarily attribute this observation to a steric influence on the post-equilibrium protonation of the $In(OTf)_3$-coordinated enolate. Another plausible reason involves a weak association between the *o*-methoxy group and the indium-coordinated enolate, which hinders *β*-face protonation and generates more of the *cis*-product. Next, the electronic effect of electron-withdrawing aryl substituents on the product outcome was examined. When the 4-nitro, 3-nitro, and 4-cyano substituted aryl groups were employed (Table 5.1, entries 3-5), the corresponding quinoline products **V-96c-e** were formed in good yields (78%, 86%, and 78%, respectively). However, lower diastereoselectivity was observed in all cases (~2:1 *dr*). Thus, a strong electronic influence on the reaction is observed when the aryl substituent is changed to a strong electron-withdrawing group. It is believed that the observed electronic effect may arise from epimerization at the benzylic C-6 position which erodes the ratio of thermodynamic *trans*-isomer. Given that C-6 is equivalent to a dibenzylic center, its hydrogen should have a pKa of ~30. When a strong electron-withdrawing group (NO_2 or CN) is placed in the *para*- or *meta*-position of the phenyl ring, the pKa of that hydrogen would drop to ~16-20. Therefore, it was anticipated that the hydrogen at C-6 would be acidic enough to undergo epimerization.

Table 5.1. An Examination of Electronic Effects of Alkene Substituents[a]



V-94 **V-96**

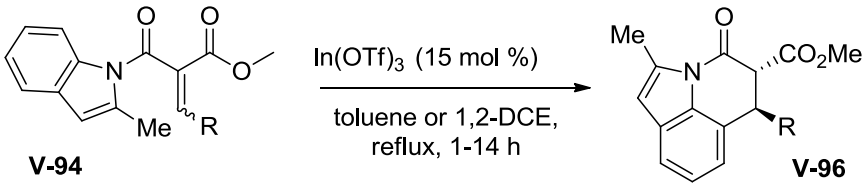
entry	R	product	time (h)	yield (%)[b]	dr[c]
1	4-$MeOC_6H_4$	 **V-96a**	3	63	50:1
2	2-$MeOC_6H_4$	 **V-96b**	3	87	3.7:1
3	4-$NO_2C_6H_4$	 **V-96c**	14	78	2.4:1
4	3-$NO_2C_6H_4$	 **V-96d**	13	86	2.2:1
5	4-CNC_6H_4	 **V-96e**	14	78	1.9:1
6	4-FC_6H_4	 **V-96f**	1	94	2.6:1
7	3-BrC_6H_4	 **V-96g**	14	61	8.3:1

[a] Conditions: Reactions using substrate **V-94** (1 equiv.) and $In(OTf)_3$ (15 mol %) in 1,2-DCE or toluene at reflux. [b] Isolated yields after column chromatography. [c] Diastereoselectivities determined from ^1H NMR of the crude reaction mixture and represent *trans/cis* diastereomeric ratio.

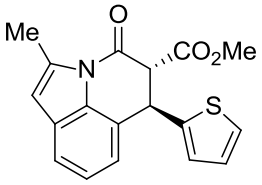
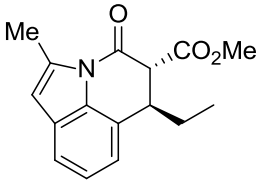
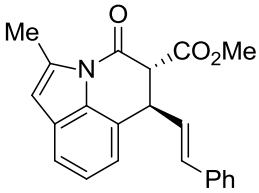
In contrast, when a strong electron donating group is present, the pKa of the hydrogen would be too high for epimerization (i.e., high *dr* for *p*-OMe). Competing epimerizations at C-5 and C-6, could account for the observed reduced diastereoselectivities. When the *p*-fluoro and *m*-bromo substituted aryl groups were used (Table 5.1, entries 6 and 7), both gave their respective products **V-96f** and **V-96g** in 94% and 61% yield. However, while the *m*-bromide gave an 8:1 *dr*, the *p*-fluoride only gave a 2.6:1 *dr*. Given fluorine's high electronegativity, a similar electronic effect may be occurring as was observed with the nitro and cyano groups.

While pleased with the results of the aromatic substrates, the reaction scope to include heteroaromatic, and nonaromatic substrates was examined. Heteroaryl substituents on the acrylate are also tolerated. In a representative example, the 2-thienyl derivative **V-94h** underwent cyclization furnishing **V-96h** as a single observable diastereomer in 51% yield (Table 5.2, entry 1). In nonaromatic substrates, the France lab was particularly interested in examining acrylates derived from alkyl aldehydes and cinnamaldehyde. When the propyl-substituted acrylate **V-94i** was subjected to the optimal reaction conditions, no conversion to the desired pyrrolo[3,2,1-*ij*]quinolines was observed even after 24 h. Thus, indicating that the nature of the alkene substituent has a significance influence on the reaction outcome. After some optimization, it was found that the cyclization could be achieved efficiently at an elevated catalyst loading in toluene at reflux. Under these new conditions, the cyclized product **V-96i** was obtained in 84% yield with 25:1 *dr* (Table 5.2, entry 2). Subjecting the cinnamaldehyde-derived acrylate **V-94j** to the same conditions, generated **V-96j** in 65% yield with 20:1 *dr* (Table 5.2, entry 3).

Table 5.2. Effect of Heteroaromatic and Non-Aromatic Alkene Substituents[a]



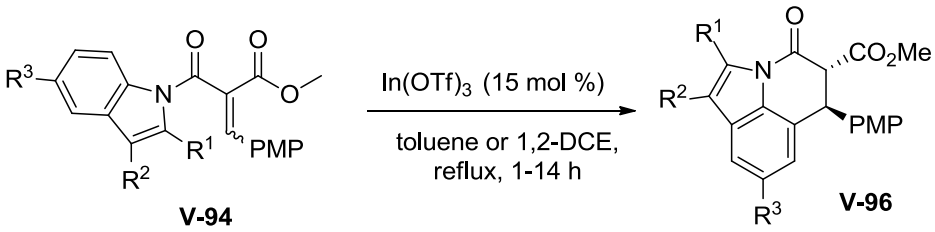
V-94 **V-96**

entry	R	product	time (h)	yield (%)[b]	dr[c]
1	2-thienyl	 **V-96h**	14	51	>99:1
2	*n*-propyl	 **V-96i**	12	84[d]	25:1
3	-CH=CHPh	 **V-96j**	14	65[d]	20:1

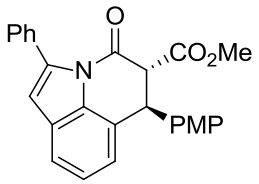
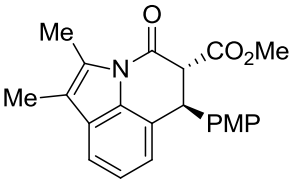
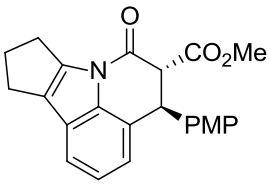
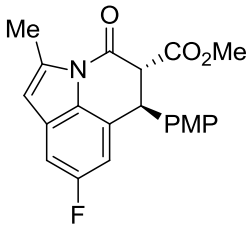
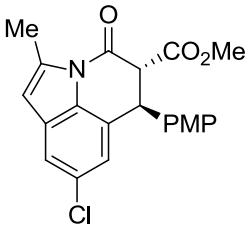
[a] Conditions: Reactions were performed with substrate 5 (1 equiv.) and $In(OTf)_3$ (15 mol %) in toluene at reflux. [b] Isolated yields after column chromatography. [c] Diastereoselectivities determined from ^1H NMR of the crude reaction mixture and represent *trans/cis* diastereomeric ratio. [d] Reaction performed with 30 mol% $In(OTf)_3$ in toluene at reflux.

Next, variation about the indole ring was examined (Table 5.3). When the 2-phenyl indolyl acrylate **V-94k** (derived from 2-phenyl indole and *p*-anisaldehyde) was subjected to the reaction conditions (Table 5.3, entry 1), pyrrolo[3,2,1-*ij*]quinolin-4-one **V-96k** was obtained in 97% yield with 17:1 *dr*. 2,3-Disubstituted indoles also performed competently in the cyclization. For example, the 2,3-dimethyl indolyl acrylate **V-94l** afforded its corresponding product **V-96l** in 80% yield with 50:1 *dr* (Table 5.3, entry 2).

Table 5.3. Effect of Substitution about Indole on the Reaction Outcome[a]



V-94 **V-96**

entry	substrate	product	time (h)	yield (%)[b]	dr[c]
1	R^1= Ph; R^2, R^3=H	 **V-96k**	3	97	17:1
2	R^1,R^2 =Me Ph; R^3=H	 **V-96l**	4	86	>99:1
3	R^1,R^2 =-$(CH_2)_3$- ; R^3=H	 **V-96m**	12	82	>99:1
4	R^1=Me; R^2=H; R^3= F	 **V-96n**	12	88[d]	>99:1
5	R^1=Me; R^2=H; R^3= Cl	 **V-96o**	4	90	>99:1

[a] Conditions: Reactions were performed with substrate **V-94** (1 equiv.) and In(OTf)$_3$ (15 mol %) in toluene at reflux. [b] Isolated yields after column chromatography. [c] Diastereoselectivities determined from ^{1}H NMR of the crude reaction mixture and represent trans/cis diastereomeric ratio. [d] Reaction performed in 1,2- DCE at reflux.

Similarly, the tetrahydrocyclopenta[*b*]indole based acrylate **V-94m** provided the tetracyclic product **V-96m** in 82% yield as a single observable diastereomer (Table 5.3, entry 3). Installing substituents on the benzenoid portion of indole was also tolerated and had no deleterious effect on the reaction outcome (Table 5.3, entries 4 and 5). For example, the 5-fluoro- and 5-chloro-2-methyl indole derivatives **V-94n** and **V-94o** fashioned corresponding pyrrolo[3,2,1-*ij*]-quinoline derivatives in high yields (80% and 82%) and high diastereoselectivities (50:1 *dr* for **V-96n** and >99:1 *dr* for **V-96o**), respectively.

As previously mentioned, the tricyclic skeletons of the 1,2,5,6-tetrahydro-4*H*-pyrrolo[3,2,1-*ij*]quinolines (lilolidines, **V-7**) have been shown to have very interesting applications. Toward this end, the reactivity of the indoline-derived substrate was investigated to determine its compatibility in the intramolecular F-C annulation (Figure 5.37). Subjecting **V-97a** to the reaction conditions provided the lilolidine derivative **V-98** in 81% yield as only one observable diastereomer in a mixture with its decarboxylated product. Due to the success of indoline, we also employed the substrate **V-97b** (derived from tetrahydroquinoline) in the cyclization (Figure 5.37). The resulting product will contain the 2,3,6,7-tetrahydro-1*H*,5*H*-benzo[*ij*]quinolizine core (also referred in the literature as 1,2,3,5,6,7-hexahydropyrido[3,2,1-*ij*]quinoline, which is present in the julolidine class of alkaloids. Thus, when **V-97a** subjected to the reaction conditions, it readily cyclized to give the tricyclic product **V-99** in 83% yield as the *trans*-diastereomer. This result is noteworthy since julolidine and its derivatives has been used as an key intermediate to synthesize various labeling reagents for carboxylic acids,[29] amines,[30] and laser dyes.[31]

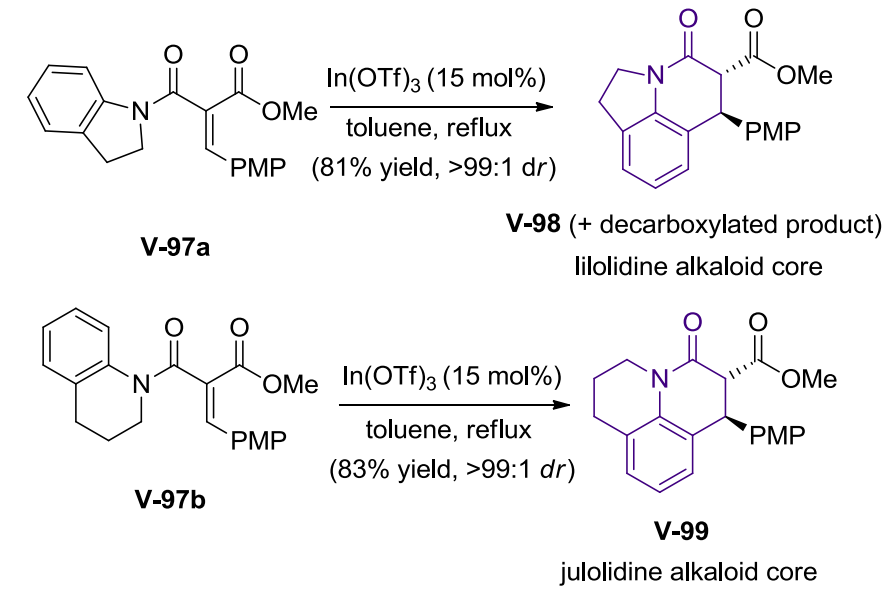


Figure 5.37. Access to the *Lilolidine* and *Julolidine* Alkaloids Skeleton

5.4. CONCLUSION

In conclusion, this study has documented a general annulation route for the efficient assembly of a variety of densely functionalized 5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-4-ones. This transformation involves an $In(OTf)_3$-induced diastereoselective Friedel-Crafts (F-C) alkylation of methyl 2-(2-methyl-1*H*-indole-carbonyl)acrylates. The products are formed in good to high yields with diastereoselectivities up to >99% *dr*. Further investigations into the observed stereoelectronic effects are currently underway. Investigations involving the use of chiral Lewis acid complexes will be reported in due course. Finally, the scope of this reaction has been demonstrated by the rapid synthesis of lilolidine and julolidine core skeletons.

5.5. EXPERIEMENTAL

5.5.1. General Methods

All reactions were carried out in pre-dried glassware from the oven and any additional moisture was removed by flame-drying the reaction vessel. Each reaction proceeded under a nitrogen atmosphere with anhydrous solvents, unless stated otherwise. Tetrahydrofuran and diethyl ether were distilled from a sodium/benzophenone ketyl under nitrogen and stored in a Schlenk flask. Benzene, toluene, 1,2-dichloroethane and dichloromethane were purified by distillation from calcium hydride. All other reagents were purchased from Acros, Sigma-Aldrich, Fluka, VWR, Merck, Alfa Aesar, TCI and Strem (for metal catalysts) and used without further purification. Compounds **V-100** were synthesized according to our reported protocol.[32]

Chromatographic purification was performed as flash chromatography with Silicycle silica gel (40-65μm). For quantitative flash chromatography, technical grades solvents were utilized. Analytical thin-layer chromatography (TLC) was performed on EMD silica gel 60 F_{254} TLC glass plates. Visualization was accomplished with UV light, aqueous basic potassium permanganate ($KMnO_4$) solution, iodine, aqueous acidic dinitrophenylhydrazine (DNP) solution, aqueous acidic *p*-anisaldehyde (PAA) solution, and an ethanol solution of phosphomolybdic acid (PMA) followed by heating. Each yield refers to an isolated, analytically-pure material.

Infrared (IR) spectra were obtained using a Nicolet 4700 FTIR with an ATR attachment from SmartOrbit Thermoelectronic Corp. The IR bands are characterized as weak (w), medium (m), and strong (s). Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Varian Mercury Vx 300 MHz

spectrometer, Varian Mercury Vx 400 MHz spectrometer or Bruker 400 MHz spectrometer with solvent resonances as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, t = triplet, m = multiplet, br = broad), coupling constants (Hz), and integration. Mass spectra were obtained using a VG-70SE instrument.

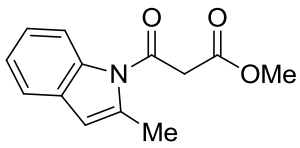
Diastereomeric ratios for cyclized products **V-96 (or V-98/V-99)** were determined by ^{1}H NMR based on comparing the signal ratios of the benzylic protons (~4.0-5.0 ppm) for the two diastereomeric protons. The first signal represents the *trans* isomer and the second signal represents the *cis* isomer. These assignments are based on the coupling constants.

5.5.2. Experimental Procedures

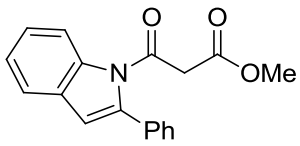
5.5.2.1. Synthesis of β-amide esters

Sodium hydride (1.2 equiv.) was suspended in THF and cooled to 0 °C. In a separate flask, the desired *N*-heterocycle (1.0 equiv.) was dissolved in THF and syringed into the reaction vessel. After 30 min, methyl-3-chloro-3-oxopropanoate (1.25 equiv.) was added quickly. The reaction was stirred for 14 h at room temperature. The reaction mixture was quenched with water. The organic layer was separated, and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced

pressure. The residue was purified by silica gel flash chromatography for product isolation.

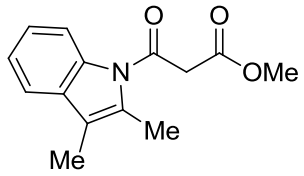


Methyl 3-(2-methyl-1*H*-indol-1-yl)-3-oxopropanoate (V-100a): The general procedure was followed using sodium hydride (1.91 g, 47.7 mmol), 2-methyl-1*H*-indole (5.00 g, 38.2 mmol), methyl-3-chloro-3-oxopropanoate (4.91 mL, 45.7 mmol), and THF (125 mL). After 14 h, the reaction was quenched, and column chromatography afforded **V-100a** as a brick red solid (6.05 g, 69%). (R_f 0.40, 30% EtOAc/Hex) [**m.p.** 74-76 °C] **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.87 - 7.92 (m, 1H), 7.43 - 7.48 (m, 1H), 7.21 - 7.28 (m, 2H), 6.39 (s, 1H), 4.07 (s, 2H), 3.81 (s, 3H), 2.61 (d, *J* = 1.12 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 166.9, 165.9, 137.0, 136.3, 129.8, 123.9, 123.6, 120.0, 114.9, 110.6, 52.7, 45.6, 17.3. **IR**: 3022.4 (w), 2953.1 (w), 1733.8 (s), 1700.1 (s), 1684.4 (s), 1606.3 (m), 1588.1 (m), 1526.9 (m), 1450.5 (m), 1374.4 (m), 1300.3 (m), 1235.7 (s), 1162.5 (m), 1085.2 (w), 758.3 (s), 668.5 (w), 649.4 (w) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 231.0895, Obs. 231.0894.



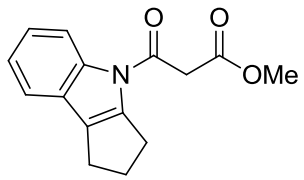
Methyl 3-oxo-3-(2-phenyl-1*H*-indol-1-yl)propanoate (V-100b): The general procedure was followed using sodium hydride (0.414 g, 17.3 mmol), 2-phenyl-1*H*-indole (3.00 g, 15.5 mmol), methyl-3-chloro-3-oxopropanoate (2.0 mL, 18.7 mmol), and THF (140 mL). After 5 h, the reaction was quenched, and column chromatography afforded **V-100b** as an

orange oil (1.28 g, 28%). (R_f 0.48, 30% EtOAc/Hex) **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 8.40 (qd, *J* = 0.84, 8.28 Hz, 1H), 7.55 - 7.59 (m, 1H), 7.44 - 7.49 (m, 5H), 7.36 - 7.41 (m, 1H), 7.29 - 7.34 (m, 1H), 6.64 (d, *J* = 0.69 Hz, 1H), 3.63 (s, 3H), 3.39 (s, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 166.8, 166.7, 139.0, 137.9, 133.3, 129.1, 129.0, 129.0, 125.5, 124.2, 120.5, 120.4, 116.3, 112.5, 52.4, 45.9. **IR**: 3029.5 (w), 2958.2 (s), 2925.4 (s), 2852.3 (s), 1745.4 (s), 1715.4 (s), 1604.8 (w), 1470.7 (m), 1451.8 (w), 1406.9 (m), 1359.4 (m), 1341.8 (w), 1301.7 (m), 1253.6 (w), 1205.1 (m), 1155.5 (m), 1117.3 (w), 1076.5 (m), 1056.7 (w), 1020.7 (w), 970.1 (m), 919.4 (w), 821.1 (w), 747.8 (m), 700.7 (w) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 293.1052, Obs. 293.1053.

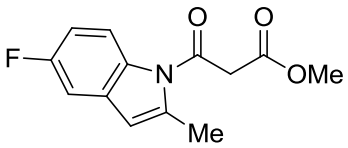


Methyl 3-(2,3-dimethyl-1*H*-indol-1-yl)-3-oxopropanoate (V-100c): The general procedure was followed using sodium hydride (0.330 g, 8.26 mmol), 2,3-dimethyl-1*H*-indole (1.00 g, 6.89 mmol), methyl-3-chloro-3-oxopropanoate (0.921 mL, 8.61 mmol), and THF (35 mL). After 14 h, the reaction was quenched, and column chromatography afforded **V-100c** as a pale yellow solid (1.05 g, 62%). (R_f 0.26, 20% EtOAc/Hex) [**m.p.** 75-77 °C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.77-7.84 (m, 1H), 7.26-7.32 (m, 1H), 7.17 (m, 2H), 3.88 (s, 2H), 3.72 (s, 3H), 2.34 (s, 3H), 2.03 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 8.2, 13.5, 45.2, 52.1, 114.5, 115.8, 117.7, 122.9, 123.6, 130.8, 131.6, 135.0, 165.3, 166.7. **IR**: 2989.2 (w), 2959.3 (w), 2925.6 (w), 1741.6 (s), 1681.3 (s), 1615.5 (w), 1449.6 (m), 1433.5 (m), 1361.6 (s), 1329.6 (m), 1259.5 (s), 1229.0 (w), 1162.2 (s), 1127.1 (m),

1100.2 (w), 1069.9 (w), 1019.5 (s), 928.9 (m), 833.2 (w), 759.5 (s), 691.3 (m), 613.1 (m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 245.1052, Obs. 245.1053.

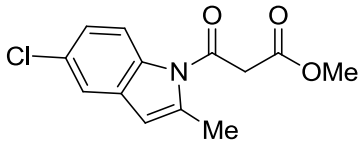


Methyl 3-(2,3-dihydrocyclopenta[*b*]indol-4(1*H*)-yl)-3-oxopropanoate (V-100d): The general procedure was followed using sodium hydride (0.764 g, 19.1 mmol), 1,2,3,4-tetrahydrocyclopenta[*b*]indole (2.5 g, 15.9 mmol), methyl-3-chloro-3-oxopropanoate (2.1 mL, 19.1 mmol), and THF (45 mL). After 16 h, the reaction was quenched, and column chromatography afforded **V-100d** as a brick red solid (3.47 g, 85%). (R_f 0.30, 25% EtOAc/Hex) [**m.p.** 120-122 °C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 8.41 (d, *J* = 5.46 Hz, 1H), 7.31 - 7.37 (m, 1H), 7.21 - 7.30 (m, 2H), 3.86 (s, 2H), 3.79 (s, 3H), 2.92 - 3.00 (m, 2H), 2.70 - 2.78 (m, 2H), 2.45 - 2.57 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 167.0, 164.3, 140.9, 128.3, 126.9, 124.7, 124.2, 123.9, 118.5, 117.3, 52.7, 43.8, 29.5, 27.6, 23.6. **IR**: 3116.2 (w), 2988.6 (w), 2947.9 (w), 2928.3 (w), 2869.6 (w), 1752.8 (s), 1693.5 (s), 1608.7 (m), 1447.9 (m), 1434.9 (s), 1379.7 (m), 1346.6 (w), 1325.2 (w), 1260.4 (s), 1161.9 (m), 1122.1 (m), 1074.0 (m), 1029.6 (m), 768.6 (s), 749.6 (m), 686.1 (m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 257.1052, Obs. 257.1045.



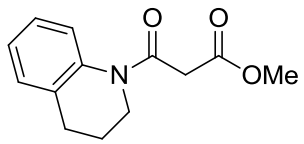
Methyl 3-(5-fluoro-2-methyl-1*H*-indol-1-yl)-3-oxopropanoate (V-100e): The general procedure was followed using potassium hydride (0.711 g, 17.7 mmol), 5-fluoro-2-methyl-1*H*-indole (2.03 g, 13.6 mmol), methyl-3-chloro-3-oxopropanoate (1.9 mL, 17.7

mmol), and THF (18 mL). After 14 h, the reaction was quenched, and column chromatography afforded **V-100e** as a red solid (0.805 g, 24%). (R_f 0.20, 20% EtOAc/Hex) [**m.p.** 80-82 °C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 7.96 (dd, *J* = 4.45, 9.11 Hz, 1H), 7.08 (dd, *J* = 2.60, 8.54 Hz, 1H), 6.95 (dt, *J* = 2.64, 9.09 Hz, 1H), 6.35 (s, 1H), 4.03 (s, 2H), 3.80 (s, 3H), 2.59 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 166.8, 165.6, 161.2, 158.0, 138.1, 133.0, 130.9, 130.8, 116.5 and 116.4 (doublet), 111.6, 111.3, 110.6 and 110.5 (doublet), 105.8, 105.4, 52.8, 45.4, 17.3. **IR**: 3013.0 (w), 2956.9 (w), 1752.2 (s), 1682.4 (s), 1603.6 (m), 1476.2 (m), 1438.8 (m), 1376.3 (m), 1301.9 (w), 1259.5 (w), 1187.8 (m), 1157.8 (s), 1129.8 (m), 1000.5 (m), 958.5 (m), 870.7 (m), 797.1 (m), 780.4 (m), 668.4 (m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 249.0801, Obs. 249.0809.



Methyl 3-(5-chloro-2-methyl-1*H*-indol-1-yl)-3-oxopropanoate (V-100f): The general procedure was followed using sodium hydride (0.2908 g, 7.27 mmol), 5-chloro-2-methyl-1*H*-indole (1.00 g, 6.06 mmol), methyl-3-chloro-3-oxopropanoate (0.811 mL, 7.57 mmol), and THF (30 mL). After 16 h, the reaction was quenched, and column chromatography afforded **V-100f** as a reddish brown solid (0.114 g, 11%). (R_f 0.25, 20% EtOAc/Hex) [**m.p.** 46-48 °C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 7.88 (dd, *J* = 0.44, 8.90 Hz, 1H), 7.35 (d, *J* = 2.05 Hz, 1H), 7.16 (dd, *J* = 2.09, 8.90 Hz, 1H), 6.27 (d, *J* = 0.62 Hz, 1H), 3.99 (s, 2H), 3.79 (s, 3H), 2.55 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 166.6, 165.6, 137.8, 134.9, 130.9, 129.1, 123.9, 119.4, 116.3, 109.9, 52.7, 45.3, 17.2. **IR**: 2993.0 (w), 2953.8 (w), 1746.0 (s), 1697.9 (s), 1594.7 (m), 1446.3 (s), 1362.6 (s), 1334.8 (m),

1309.2 (m), 1254.0 (s), 1159.8 (s), 1075.0 (w), 1041.4 (w), 1000.9 (w), 919.6 (w), 807.6 (w), 723.6 (w) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 265.0501, Obs. 265.0499.

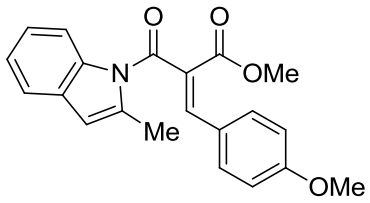


Methyl 3-(3,4-dihydroquinolin-1(2*H*)-yl)-3-oxopropanoate (V-100g): A mixture of potassium carbonate (6.23 g, 44.0 mmol) and 1,2,3,4-tetrahydroquinoline (3.0 g, 22.5 mmol), methyl-3-chloro-3-oxopropanoate (2.7 mL, 24.8 mmol) and acetonitrile (60 mL) were heated to reflux. After 14 h, the reaction mixture was cooled, filtered and dried *in vacuo.* The residue was dissolved in EtOAc/Hex (1:2.5). The organic layer was separated, and the aqueous layer was extracted three times with EtOAc. The combined organic layers were dried with anhydrous sodium sulfate, filtered, and concentrated. Column chromatography afforded **V-100g** as a reddish orange oil (3.76 g, 72%). (R_f 0.30, 25% EtOAc/Hex) **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 7.07 - 7.19 (m, 4H), 3.74 - 3.83 (m, 2H), 3.65 (s, 3H), 3.58 (s, 2H), 2.69 (t, *J*=6.49 Hz, 2H), 1.94 (quin, *J*=6.65 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 168.1, 165.5, 128.4, 126.3, 125.8, 123.9, 52.2, 42.7, 41.4, 26.4, 23.7. **IR**: 3004.1 (w), 2951.0 (w), 2889.1 (w), 1739.3 (s), 1651.4 (s), 1603.6 (w), 1580.9 (w), 1491.8 (s), 1435.5 (w), 1386.9 (m), 1326.1 (w), 1201.5 (m), 1155.7 (m), 1074.0 (w), 1019.9 (m), 949.0 (w), 763.0 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 233.1052, Obs. 233.1031.

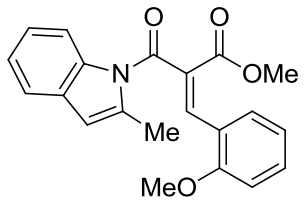
5.5.2.2. Preparation of Acrylates

General Method A:[33] The β-ester-amide (1.0 equiv.), aldehyde (1.3 equiv.), glacial acetic acid (0.5 equiv.), and piperidine (0.1 equiv.) were heated to a reflux in benzene using a Dean-Stark trap for 14 h. After cooling the reaction mixture to room temperature, water was added to the reaction vessel, and the organic layer was collected. Subsequently, the aqueous phase was extracted with EtOAc three times. The combined organic layers were washed with 1M HCl and saturated sodium bicarbonate. The combined organic layers were dried with Na_2SO_4, filtered, concentrated, and purified by silica gel column chromatography (gradient EtOAc/Hex).

General Method B:[34] A round bottom flask was charged with the β-ester-amide (1.0 equiv.) and THF (25 mL). After cooling the solution to 0 °C, titanium(IV) chloride tetrahydrofuran complex (2.0 equiv.) and CCl_4 (2.0 equiv.) were added to the reaction vessel. After 1 h at 0 °C, the aldehyde (1.0 equiv.) was added slowly, and the reaction was stirred for an hour. Then, pyridine (4.0 equiv.) was added to the solution drop-wise. The reaction mixture was warmed to room temperature and allowed to stir for 14 h. The reaction was quenched with water and the organic layer was collected. The aqueous layer was extracted with ether, and the combined organic layers were washed with saturated $NaHCO_3$ and brine. The organic layer was dried with Mg_2SO_4, filtered, concentrated, and purified by silica gel column chromatography (gradient EtOAc/Hex).

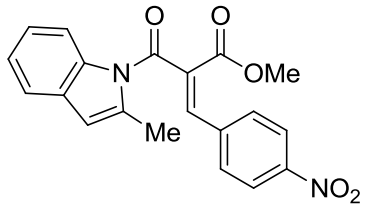


(*Z*)-Methyl 3-(4-methoxyphenyl)-2-(2-methyl-1*H*-indole-1-carbonyl)acrylate (V-94a): Methyl 3-(2-methyl-1*H*-indol-1-yl)-3-oxopropanoate (1.80 g, 7.78 mmol), 4-methoxybenzaldehyde (1.2 mL, 10.1 mmol), glacial acetic acid (0.262 g, 4.37 mmol), piperidine (80 µL , 0.810 mmol) and benzene (120 mL) were mixed according to general method A to afford **V-94a** as an orange oil (2.50 g, 92%) after 18 h (R_f 0.24, 20% EtOAc/Hex) (*Diastereomer!*) **^{1}H NMR** (300 MHz, $CDCl_3$*)* δ ppm 8.43 (br. s., 0.81), 7.87 (s, 1.13), 7.72 (s, 0.15), 7.33 - 7.47 (m, 3.50), 7.21 - 7.30 (m, 2.08), 6.89 (d, *J* = 8.79 Hz, 0.27), 6.75 (d, *J* = 8.76 Hz, 2.10), 6.35 (s, 1.00), 3.87 (d, *J* = 0.70 Hz, 0.25), 3.83 (s, 0.26), 3.81 (s, 0.31), 3.77 (s, 2.63), 3.72 (s, 2.94), 2.48 (br. s., 2.87). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 166.3, 165.1, 161.8, 142.9, 142.5, 131.9, 131.4, 129.8, 125.6, 124.7, 119.6, 114.5, 114.3, 55.2, 52.7, 16.7. **IR:** 3065.3 (w), 2951.7 (w), 2939.1 (w), 1720.6 (s), 1682.4 (s), 1600.9 (s), 1511.8 (s), 1452.5 (s), 1385.8 (m), 1321.3 (m), 1290.4 (m), 1258.9 (s), 1203.7 (m), 1172.3 (s), 1123.0 (m), 1056.1 (w), 1027.6 (m), 917.2 (w), 831.4 (m), 763.9 (s), 751.0 (s), 700.6 (m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 349.1314, Obs. 349.1319.



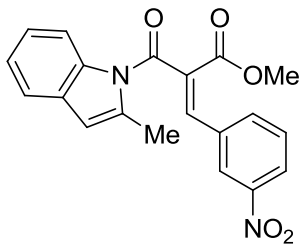
(*Z*)-Methyl 3-(2-methoxyphenyl)-2-(2-methyl-1H-indole-1-carbonyl)acrylate (V-94b): Methyl 3-(2-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.200 g, 0.865 mmol), 2-methoxybenzaldehyde (0.153 g, 1.12 mmol), glacial acetic acid (0.026 g, 0.433 mmol), piperidine (0.0147 g, 0.173 mmol) and benzene (20 mL) were mixed according to general method A to afford **V-94b** as a yellow solid (0.231 g, 75%) after 18 h (R_f 0.69, 30% EtOAc/Hex) [**m.p.** 102-104 °C] (*Temperature for the ^{1}H NMR and ^{13}C NMR = 70 °C).*

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.30 (s, 1H), 8.22 (d, *J* = 7.28 Hz, 1H), 7.43 - 7.48 (m, 1H), 7.36 - 7.42 (m, 1H), 7.28 - 7.34 (m, 1H), 7.22 - 7.28 (m, 2H), 6.87 (d, *J* = 8.34 Hz, 1H), 6.82 (t, *J* = 7.84 Hz, 1H), 6.36 (s, 1H), 3.83 (s, 3H), 3.74 (s, 3H), 2.60 (d, *J* = 0.94 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 165.9, 165.2, 158.3, 139.7, 137.1, 132.2, 130.2, 129.9, 129.2, 123.8, 123.5, 122.2, 120.9, 119.6, 115.6, 111.2, 110.0, 55.3, 52.4, 16.5. **IR**: 3051.9 (w), 3003.8 (w), 2951.9 (m), 2840.2 (m), 1713.4 (s), 1680.3 (s), 1618.7 (m), 1596.8 (s), 1574.7 (m), 1487.0 (m), 1455.4 (s), 1435.7 (s), 1383.5 (s), 1307.0 (s), 1261.0 (s), 1240.3 (s), 1194.9 (s), 1164.3 (m), 1116.8 (m), 1083.5 (m), 1050.6 (w), 1024.7 (m), 993.0 (w), 840.3 (w), 804.0 (w), 749.2 (s), 730.4 (s), 648.0 (w) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 349.1314, Obs. 349.1315.

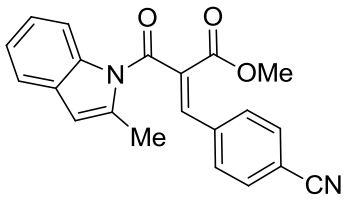


(*Z*)-Methyl 2-(2-methyl-1*H*-indole-1-carbonyl)-3-(4-nitrophenyl)acrylate (V-94c): Methyl 3-(2-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.300 g, 1.30 mmol), 4-nitrobenzaldehyde (0.255 g, 1.69 mmol), glacial acetic acid (0.0357 g, 0.596 mmol), piperidine (14.0 µL, 0.130 mmol) and benzene (25 mL) were mixed according to general method A to afford **V-94c** as a orange solid (0.300 g, 64%) after 18 h (R_f 0.45, 20% EtOAc/Hex) [**m.p.** 109-111 °C] (*Temperature for the ^{1}H NMR and ^{13}C NMR = 70 °C).* **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 8.03 - 8.09 (m, 3H), 7.94 (s, 1H), 7.49 - 7.54 (m, 2H), 7.38 - 7.42 (m, 1H), 7.20 - 7.25 (m, 2H), 6.34 (d, *J* = 0.94 Hz, 1H), 3.85 (s, 3H), 2.51 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 164.4, 164.0, 148.8, 139.9, 138.5, 136.7, 132.8, 130.0, 129.9, 124.3, 124.1, 123.9, 120.0, 115.0, 111.2, 52.9, 16.4. **IR**:

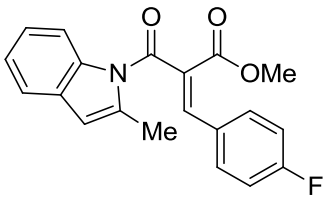
3108.3 (w), 2953.4 (w), 2929.6 (w), 1726.0 (s), 1678.5 (s), 1596.9 (m), 1521.3 (s), 1456.1 (s), 1436.1 (m), 1384.8 (s), 1291.1 (s), 1256.0 (s), 1200.9 (s), 1111.8 (w), 1083.9 (w), 1027.5 (w), 992.3 (w), 852.1 (w), 825.8 (w), 749.1 (s), 691.0 (w) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 364.1059, Obs. 364.1076.



(*Z*)-Methyl 2-(2-methyl-1*H*-indole-1-carbonyl)-3-(3-nitrophenyl)acrylate (V-94d): Methyl 3-(2-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.350 g, 1.513 mmol), 3-nitrobenzaldehyde (0.297 g, 1.97 mmol), glacial acetic acid (0.0417 g, 0.696 mmol), piperidine (15 µL , 0.151 mmol) and benzene (20 mL) were mixed according to general method A to afford **V-94d** as a pale yellow solid (0.220 g, 40 %) after 20 h. (R_f 0.40, 20% EtOAc/Hex) [**m.p.** 112-114 °C] (*Temperature for the ^{1}H and ^{13}C = 60 °C)* **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 8.21 - 8.24 (m, 1H), 8.10 (ddd, *J* = 1.00, 2.16, 8.25 Hz, 1H), 8.03 (br. s., 1H), 7.94 (s, 1H), 7.63 - 7.67 (m, 1H), 7.35 - 7.41 (m, 2H), 7.18 - 7.25 (m, 2H), 6.33 (d, *J* = 0.88 Hz, 1H), 3.86 (s, 3H), 2.54 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 164.6, 164.2, 148.7, 139.9, 136.7, 134.4, 134.2, 132.1, 130.1, 130.0, 124.9, 124.3, 124.2, 124.2, 120.0, 115.1, 111.3, 53.1, 16.7. **IR**: 3083.4 (w), 2954.9 (w), 2928.5 (w), 1727.7 (s), 1678.7 (s), 1630.1 (w), 1597.5 (w), 1576.9 (w), 1532.1 (s), 1456.4 (s), 1437.6 (m), 1386.4 (s), 1351.2 (s), 1308.8 (s), 1258.6 (s), 1203.4 (s), 1086.2 (w), 1027.7 (w), 992.8 (w), 824.9 (w), 808.9 (w), 751.6 (m), 736.8 (m), 676.3 (w) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 364.1059, Obs. 364.1065

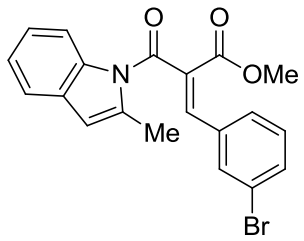


(*Z*)-Methyl 3-(4-cyanophenyl)-2-(2-methyl-1*H*-indole-1-carbonyl)acrylate (V-94e): Methyl 3-(2-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.350 g, 1.51 mmol), 4-cyanobenzaldehyde (0.258 g, 1.97 mmol), glacial acetic acid (0.0417 g, 0.696 mmol), piperidine (15 µL , 0.151 mmol) and benzene (20 mL) were mixed according to general method A to afford **V-94e** as a off-white solid (0.325 g, 62%) after 18 h. (R_f 0.35, 20% EtOAc/Hex) [m.p. 122-124 °C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 8.81 - 8.05 (br. s., 1H), 7.38 - 7.53 (m, 6H), 7.20 - 7.28 (m, 2H), 6.35 (s, 1H), 3.82 (s, 3H), 2.46 (br. s., 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 164.6, 164.0, 140.4, 136.4, 132.5, 131.5, 129.6, 124.2, 119.9, 117.7, 113.8, 111.2, 53.1, 16.7. **IR**: 3056.6 (w), 2954.9 (w), 2928.2 (w), 2229.5 (m), 1725.7 (s), 1677.7 (s), 1627.5 (m), 1596.9 (m), 1576.6 (m), 1504.2 (w), 1456.0 (s), 1435.5 (m), 1384.3 (s), 1303.3 (s), 1256.1 (s), 1201.7 (s), 1152.5 (w), 1117.1 (w), 1084.3 (m), 1027.4 (m), 992.3 (m), 936.0 (w), 830.2 (m), 750.5 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 344.1161, Obs. 344.1169.



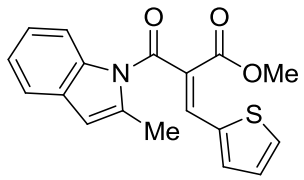
(*Z*)-Methyl 3-(4-fluorophenyl)-2-(2-methyl-1*H*-indole-1-carbonyl)acrylate (V-94f): Methyl 3-(2-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.350 g, 1.51 mmol), 4-fluorobenzaldehyde (0.210 mL, 2.00 mmol), glacial acetic acid (0.0417 g, 0.695 mmol), piperidine (15 µL, 0.151 mmol) and benzene (25 mL) were mixed according to general

method A to afford **V-94f** as a yellow solid (0.293 g, 57%) after 18 h (R_f 0.40, 20% EtOAc/Hex) [**m.p.** 76-78 °C] (*Temperature for the ^{1}H and ^{13}C = 60 °C)* **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 8.20 (br. s., 1H), 7.89 (s, 1H), 7.34 - 7.45 (m, 3H), 7.17 - 7.30 (m, 2H), 6.92 (t, *J* = 8.59 Hz, 2H), 6.34 (s, 1H), 3.80 (s, 3H), 2.50 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 165.7, 165.5, 164.7, 162.4, 141.8, 136.9, 131.9 and 131.7 (doublet), 129.9, 124.2 and 124.0 (doublet), 119.8, 116.4, 116.1, 115.5, 110.9, 52.7, 16.6. **IR**: 3076.2 (w), 2951.8 (w), 1724.8 (s), 1683.9 (s), 1627.8 (w), 1598.7 (s), 1508.9 (s), 1456.5 (s), 1436.7 (m), 1386.76 (s), 1301.0 (m), 1260.4 (s), 1197.7 (s), 1162.4 (s), 834.7 (m), 750.5 (s), 668.5 (m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 337.1114, Obs. 349.1107.

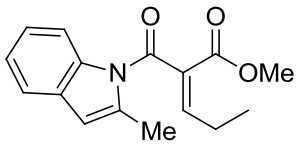


(*Z*)-Methyl 3-(3-bromophenyl)-2-(2-methyl-1*H*-indole-1-carbonyl)acrylate (V-94g): Methyl 3-(2-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.350 g, 1.51 mmol), 3-bromobenzaldehyde (0.230 mL, 1.97 mmol), glacial acetic acid (0.0417 g, 0.696 mmol), piperidine (15 µL , 0.151 mmol) and benzene (20 mL) were mixed according to general method A to afford **V-94g** as a pale gray solid (0.430 g, 72 %) after 18 h. (R_f 0.40, 20% EtOAc/Hex). [**m.p.** 107-109 °C] (*Temperature for the ^{1}H and ^{13}C = 60 °C)* **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 8.08 - 8.19 (m, 1H), 7.86 (s, 1H), 7.52 - 7.56 (m, 1H), 7.39 - 7.44 (m, 2H), 7.27 - 7.33 (m, 1H), 7.21 - 7.27 (m, 2H), 7.05 - 7.11 (m, 1H), 6.35 (d, *J* = 0.75 Hz, 1H), 3.85 (s, 3H), 2.54 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 165.0, 164.4, 141.2, 136.8, 136.5, 134.5, 133.5, 132.5, 130.5, 130.3, 130.0, 127.5, 124.2, 124.0,

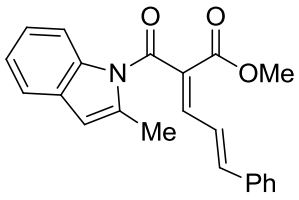
123.0, 119.8, 115.3, 111.0, 52.8, 16.6. **IR**: 2962.5 (w), 2926.4 (w), 1726.6 (s), 1681.3 (s), 1625.7 (m), 1596.8 (w), 1561.3 (w), 1456.4 (s), 1435.7 (m), 1384.9 (s), 1311.0 (s), 1258.9 (s), 1198.1 (s), 1076.9 (w), 1027.7 (w), 994.3 (w), 786.6 (w), 750.3 (s), 680.8 (w) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 397.0314, Obs. 397.0316.



(*Z*)-Methyl 2-(2-methyl-1*H*-indole-1-carbonyl)-3-(thiophen-2-yl)acrylate (V-94h): Methyl 3-(2-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.350 g, 1.51 mmol), thiophene-2-carbaldehyde (0.220 g, 1.97 mmol), glacial acetic acid (0.0417 g, 0.696 mmol), piperidine (15 µL , 0.150 mmol) and benzene (20 mL) were mixed according to general method A to afford **V-94h** as a off-white solid (0.396 g, 81%) after 18 h. (R_f 0.45, 20% EtOAc/Hex) [**m.p.** 153-155 °C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 8.28 (br. s., 1H), 8.04 (d, *J* = 0.37 Hz, 1H), 7.42 - 7.48 (m, 1H), 7.36 (d, *J* = 5.06 Hz, 1H), 7.29 - 7.33 (m, 1H), 7.23 - 7.29 (m, 2H), 6.95 - 7.00 (m, 1H), 6.39 (s, 1H), 3.79 (s, 3H), 2.50 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 165.3, 164.9, 136.9, 135.7, 135.1, 134.6, 132.5, 129.9, 128.0, 124.9, 124.2, 124.0, 119.7, 115.9, 111.0, 108.0, 52.8, 16.8. **IR**: 3104.8 (w), 2952.1 (w), 2927.5 (w), 1719.0 (s), 1675.8 (s), 1611.7 (s), 1455.9 (s), 1385.9 (s), 1342.5 (m), 1303.5 (s), 1253.5 (s), 1202.6 (s), 1086.3 (w), 1051.6 (w), 1027.9 (w), 992.9 (w), 858.1 (w), 750.5 (s), 717.4 (m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 325.0773, Obs. 325.0780.

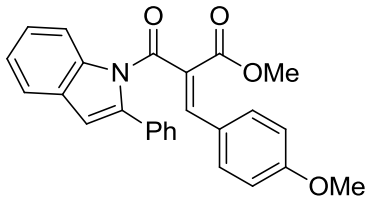


(*Z*)-methyl 2-(2-methyl-1*H*-indole-1-carbonyl)pent-2-enoate (V-94i): Methyl 3-(2-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.500 g, 2.16 mmol), propanaldehyde (0.155 mL, 2.16 mmol), $TiCl_4$•THF (1.44 g, 4.32 mmol), CCl_4 (0.418 mL, 4.32 mmol), pyridine (0.699 mL, 8.65 mmol) and THF (35 mL) were combined according to general method B to yield **V-94i** as a clear oil (0.421 g, 72%) after 14 h. (R_f 0.55, 20% EtOAc/Hex). **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 8.13 (br. s., 1H), 7.50 - 7.58 (m, 1H), 7.27 - 7.36 (m, 3H), 6.48 (d, *J* = 0.77 Hz, 1H), 3.82 (s, 3H), 2.60 (s, 3H), 2.28 (quin, *J* = 7.63 Hz, 2H), 1.13 (t, *J* = 7.53 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 165.1, 164.2, 150.7, 136.8, 136.5, 131.5, 129.8, 123.8, 123.7, 119.8, 115.2, 110.4, 52.5, 23.1, 16.9, 12.3. **IR**: 2973.6 (w), 2936.1 (w), 1726.6 (s), 1685.9 (s), 1643.0 (w), 1596.5 (w), 1575.5 (w), 1456.3 (s), 1436.9 (m), 1384.1 (s), 1310.8 (s), 1289.7 (s), 1243.9 (s), 1205.4 (w), 1036.7 (w), 989.8 (w), 783.4 (w), 750.3 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 271.1208, Obs. 271.1218.



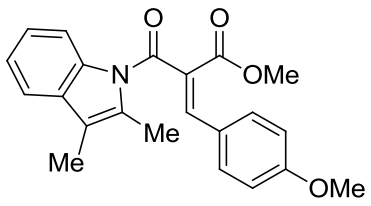
(2*Z*, 4*E*)-Methyl 2-(2-methyl-1*H*-indole-1-carbonyl)-5-phenylpenta-2,4-dienoate (V-94j): Methyl 3-(2-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.300 g, 1.30 mmol), cinnamaldehyde (0.21 mL, 1.69 mmol), glacial acetic acid (0.0357 g, 0.596 mmol), piperidine (13.97 µL, 0.1297 mmol) and benzene (25 mL) were mixed according to general method A to afford **V-94j** as a reddish orange oil (0.256 g, 57%) after 20 h. (R_f

0.48, 20% EtOAc/Hex) **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 8.10 - 8.18 (m, 1H), 7.76 (d, *J* = 11.73 Hz, 1H), 7.45 - 7.51 (m, 1H), 7.34 - 7.42 (m, 2H), 7.23 - 7.34 (m, 5H), 7.12 (d, *J* = 15.39 Hz, 1H), 6.82 - 6.95 (m, 1H), 6.42 (s, 1H), 3.74 (s, 3H), 2.54 (d, *J* = 0.99 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 165.1, 164.8, 145.4, 145.0, 136.7, 136.6, 135.1, 130.0, 129.7, 129.7, 129.0, 128.8, 128.5, 127.8, 123.9, 123.7, 122.2, 119.8, 115.3, 110.4, 52.6, 16.7. **IR**: 3030.0 (w), 2949.9 (w), 1721.0 (s), 1682.4 (s), 1614.7 (m), 1590.8 (m), 1456.2 (s), 1435.3 (m), 1384.9 (s), 1308.3 (s), 1278.6 (s), 1237.6 (s), 1202.0 (w), 1077.2 (w), 993.8 (w), 836.1 (w), 750.7 (s), 691.5 (w) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 345.1365, Obs. 345.1383.

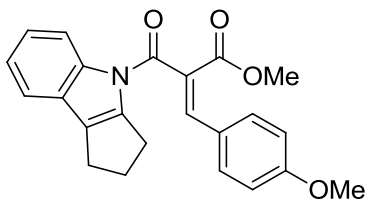


(*Z*)-Methyl 3-(4-methoxyphenyl)-2-(2-phenyl-1*H*-indole-1-carbonyl)acrylate (V-94k): Methyl 3-oxo-3-(2-phenyl-1*H*-indol-1-yl)propanoate (1.28 g, 4.36 mmol), 4-methoxybenzaldehyde (0.70 mL, 5.75 mmol), glacial acetic acid (0.131 g, 2.18 mmol), piperidine (50 μL, 0.506 mmol) and benzene (120 mL) were mixed according to general method A to afford **V-94k** as a dark brown solid (0.456 g, 25%) after 18 h. (R_f 0.37, 20% EtOAc/Hex) [**m.p.** 105-107 °C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 8.63 (d, *J* = 8.17 Hz, 1H), 7.40 - 7.51 (m, 2H), 7.29 - 7.38 (m, 2H), 7.19 - 7.27 (m, 2H), 7.16 (s, 1H), 7.00 - 7.13 (m, 4H), 6.54 - 6.61 (m, 2H), 6.34 (s, 1H), 3.73 (s, 3H), 3.71 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 166.8, 164.4, 161.5, 143.1, 139.8, 138.2, 133.4, 131.6, 129.6, 128.6, 127.8, 125.4, 125.2, 125.0, 124.3, 120.2, 116.6, 114.0, 111.9, 55.3, 52.3. **IR**: 3065.3 (w), 2951.7 (w), 2939.1 (w), 1720.6 (s), 1682.4 (s), 1600.9 (s), 1511.8 (s), 1452.5 (s), 1385.8

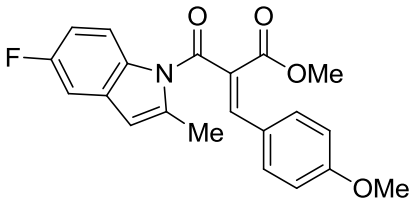
(m), 1321.3 (m), 1290.4 (m), 1258.9 (s), 1203.7 (m), 1172.3 (s), 1123.0 (m), 1056.1 (w), 1027.6 (m), 917.2 (w), 831.4 (m), 763.9 (s), 751.0 (s), 700.6 (m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 411.1471, Obs. 411.1480.



(*Z*)-Methyl 2-(2,3-dimethyl-1*H*-indole-1-carbonyl)-3-(4-methoxyphenyl)acrylate (V-94l): Methyl 3-(2,3-dimethyl-1*H*-indol-1-yl)-3-oxopropanoate (1.00 g, 4.08 mmol), 4-methoxybenzaldehyde (0.617 mL, 5.10 mmol), glacial acetic acid (0.112 g, 1.88 mmol), piperidine (0.0340 g, 0.407 mmol) and benzene (35 mL) were mixed according to general method A to afford **V-94l** as a yellow solid (1.080 g, 73%) after 18 h. (R_f 0.25, 20% EtOAc/Hex) [**m.p.** 94-96 °C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 8.63 (br. s, 1H), 7.87 (br. s., 1H), 7.33 - 7.48 (m, 3H), 7.28 (br. s., 2H), 6.73 (d, *J* = 8.50 Hz, 2H), 3.77 (s, 3H), 3.67 (d, *J* = 1.21 Hz, 3H), 2.25 - 2.53 (m, 3H), 2.15 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 165.9, 165.2, 161.9, 142.5, 136.1, 131.8, 131.5, 126.6, 125.3, 124.3, 123.6, 117.9, 116.5, 114.6, 55.2, 52.4, 13.4, 8.6. **IR**: 3008.4 (w), 2933.3 (w), 2839.7 (w), 1721.5 (s), 1675.4 (s), 1601.6 (s), 1513.5 (s), 1458.5 (s), 1396.3 (m), 1306.8 (s), 1258.4 (s), 1203.4 (m), 1174.8 (s), 1133.5 (w), 1028.0 (w), 907.9 (w), 832.0 (w), 750.0 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 363.1471, Obs. 363.1470.

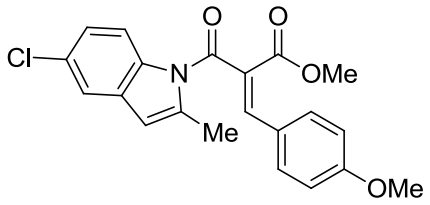


(*Z*)-Methyl 3-(4-methoxyphenyl)-2-(1,2,3,4-tetrahydrocyclopenta[*b*]indole-4-carbonyl)acrylate (V-94m): Methyl 3-(2,3-dihydrocyclopenta[*b*]indol-4(1*H*)-yl)-3-oxopropanoate (0.175 g, 0.681 mmol), 4-methoxybenzaldehyde (0.107 mL, 0.885 mmol), glacial acetic acid (0.0187 g, 0.313 mmol), piperidine (6.8 µL, 0.0680 mmol) and benzene (15 mL) were mixed according to general method A to afford **V-94m** as a white solid (0.0520 g, 20%) after 18 h. (R_f 0.40, 20% EtOAc/Hex) [**m.p.** 156-158 °C] **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 8.64 - 8.72 (m, 1H), 7.82 (s, 1H), 7.24 - 7.44 (m, 5H), 6.75 - 6.82 (m, 2H), 3.80 (s, 3H), 3.75 (s, 3H), 2.60 - 2.80 (m, 4H), 2.25 - 2.50 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 165.5, 165.3, 161.8, 142.9, 141.7, 140.9, 132.0, 128.1, 127.4, 124.9, 124.5, 124.3, 124.2, 118.5, 117.7, 114.7, 55.3, 52.7, 28.9, 27.5, 23.8. **IR**: 2950.7 (w), 2857.5 (w), 1720.8 (m), 1681.7 (s), 1602.0 (s), 1513.5 (s), 1450.13 (m), 1392.8 (m), 1258.2 (s), 1173.02 (s), 1120.5 (w), 1103.5 (w), 1043.3 (w), 983.9 (w), 831.7 (w), 751.0 (m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 375.1448, Obs. 375.1474.



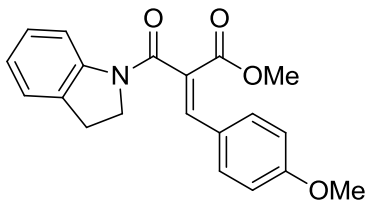
(*Z*)-Methyl 2-(5-fluoro-2-methyl-1*H*-indole-1-carbonyl)-3-(4-methoxyphenyl) acrylate (V-94n): Methyl 3-(5-fluoro-2-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.301 g, 1.21 mmol), 4-methoxybenzaldehyde (0.180 mL, 1.48 mmol), glacial acetic acid (0.0520 g, 0.873 mmol), piperidine (25 µL , 0.253 mmol) and benzene (30 mL) were mixed according to general method A to afford **V-94n** as a pale brick solid (0.382 g, 86%) after 18 h. (R_f 0.43, 30% EtOAc/Hex) [**m.p.** 95-97 °C] (*Temperature for the ^{1}H and ^{13}C = 60 °C)* **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 8.25 (br s, 1H), 7.85 (s, 1H), 7.28 -

7.39 (m, 2H), 7.05 (dd, *J* = 2.57, 8.61 Hz, 1H), 6.95 (dt, *J* = 2.58, 9.12 Hz, 1H), 6.70 - 6.79 (m, 2H), 6.27 (s, 1H), 3.78 (s, 3H), 3.71 (s, 3H), 2.46 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 166.0, 165.0, 162.1, 161.5, 158.3, 143.0, 133.3, 131.8, 131.1 and 131.0 (doublet), 125.8, 124.9, 116.9, 114.6, 111.5, 111.2, 110.3, 105.5, 105.2, 55.2, 52.5, 16.5. **IR**: 2948.8 (w), 2903.6 (w), 1720.7 (m), 1685.4 (m), 1602.5 (s), 1513.7 (s), 1472.7 (m), 1448.5 (m), 1389.2 (m), 1301.5 (m), 1274.6 (s), 1260.5 (s), 1176.5 (s), 995.0 (w), 957.3 (w), 832.8 (w), 764.3 (s), 750.0 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 367.1208, Obs. 367.1226.

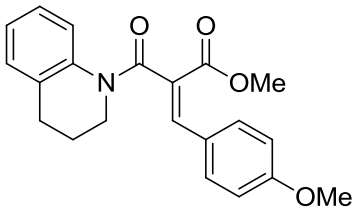


(*Z*)-Methyl 2-(5-chloro-2-methyl-1*H*-indole-1-carbonyl)-3-(4-methoxyphenyl) acrylate (V-94o): Methyl 3-(5-chloro-2-methyl-1*H*-indol-1-yl)-3-oxopropanoate (0.565 g, 2.14 mmol), 4-methoxybenzaldehyde (0.337 mL, 2.77 mmol), glacial acetic acid (0.0589 g, 0.982 mmol), piperidine (21 µL, 0.214 mmol) and benzene (30 mL) were mixed according to general method A to afford **V-94o** as a off-white solid (0.300 g, 37%) after 20 h. (R_f 0.40, 20% EtOAc/Hex) [**m.p.** 111-113 °C] (*Temperature for the ^{1}H and ^{13}C = 60 °C)* **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 8.20 (d, *J* = 8.54 Hz, 1H), 7.86 (s, 1H), 7.30 - 7.40 (m, 3H), 7.20 (dd, *J* = 2.11, 8.85 Hz, 1H), 6.72 - 6.79 (m, 2H), 6.26 (s, 1H), 3.78 (s, 3H), 3.70 - 3.75 (m, 3H), 2.47 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 166.1, 164.9, 162.1, 143.2, 138.0, 135.4, 131.8, 131.2, 129.5, 125.8, 124.9, 124.1, 119.3, 116.7, 114.7, 109.8, 55.2, 52.5, 16.5. **IR**: 2952.3 (w), 2839.8 (w), 2360.1 (m), 2342.4 (m), 1718.7 (s), 1683.4 (s), 1597.9 (s), 1512.5 (s), 1442.9 (s), 1385.6 (s), 1345.9 (w), 1294.5

(m), 1255.6 (s), 1201.3 (m), 1171.5 (s), 1124.2 (w), 1072.5 (w), 1021.4 (w), 995.1 (w), 914.0 (w), 829.9 (m), 800.5 (w), 732.0 (w), 668.6 (w) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 383.0924, Obs. 383.0922.



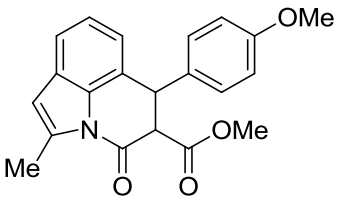
Methyl 2-(indoline-1-carbonyl)-3-(4-methoxyphenyl)acrylate (V-97a): Methyl 3-(indolin-1-yl)-3-oxopropanoate (0.350 g, 1.60 mmol), 4-methoxybenzaldehyde (0.252 mL, 2.08 mmol), glacial acetic acid (0.0440 g, 0.734 mmol), piperidine (16 µL, 0.160 mmol) and benzene (30 mL) were mixed according to general method A to afford **V-97a** as an orange oil (0.390 g, 72%) after 20 h. (R_f 0.35, 20% EtOAc/Hex) (*Diastereomers!)* **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 8.41 (d, *J* = 8.03 Hz, 1.00), 7.82 (s, 0.20), 7.70 (s, 1.14), 7.43 - 7.54 (m, 2.47), 7.28 - 7.33 (m, 0.81), 7.16 - 7.22 (m, 1.27), 7.01 - 7.13 (m, 1.44), 6.80 - 6.88 (m, 2.53), 4.36 - 4.50 (m, 0.18), 4.18 - 4.31 (m, 0.20), 3.94 (br.s., 1.16), 3.83 (s, 3.16), 3.61 - 3.80 (m, 3.87), 3.71 - 3.76 (m, 1.78), 2.92 - 3.22 (m, 2.49). **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 165.4, 165.0, 161.9, 142.6, 142.4, 140.6, 132.0, 131.8, 127.7, 126.0, 125.8, 124.6, 124.4, 117.5, 114.8, 114.5, 55.3, 52.4, 48.4, 28.0. **IR**: 3004.8 (w), 2951.7 (w), 2839.7 (w), 1716.9 (s), 1645.7 (s), 1598.9 (s), 1512.6 (s), 1482.3 (s), 1413.3 (m), 1255.3 (s), 1174.5 (s), 1126.4 (m), 1057.9 (m), 1027.4 (m), 832.3 (m), 755.8 (s), 668.5 (m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 337.1314, Obs. 337.1319.



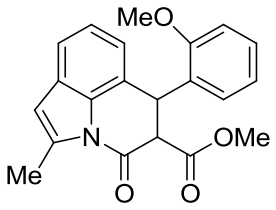
(*Z*)-Methyl 3-(4-methoxyphenyl)-2-(1,2,3,4-tetrahydroquinoline-1-carbonyl)acrylate (V-97b): Methyl 3-(3,4-dihydroquinolin-1(2*H*)-yl)-3-oxopropanoate (0.3500 g, 1.5010 mmol), 4-methoxybenzaldehyde (0.2370 mL, 1.9510 mmol), glacial acetic acid (0.0414 g, 0.6900 mmol), piperidine (14.80 µL, 0.1501 mmol) and benzene (30 mL) were mixed according to general method A to afford **V-97b** as a orange oil (0.4230 g, *Crude* = 80.19 %) after 15 h. R_f 0.35 (20% EtOAc/Hex). **HRMS (ESI)** M/Z+ Calc. 351.1471, Obs. 351.1499.

5.5.2.3. $In(OTf)_3$-Catalyzed Cyclizations

General Procedure: To a mixture of $In(OTf)_3$ (0.10-0.15 equiv.) in 1,2-DCE (or toluene) heated to a reflux, dissolved **V-94 (or V-97)** (1.0 equiv.) was syringed into the reaction vessel. The reaction was monitored by TLC and quenched with water. The phases were separated, and the product was extracted from the aqueous phase with DCM. The combined organic layers were washed with brine, dried over Mg_2SO_4, filtered, and concentrated for column chromatography using silica gel.

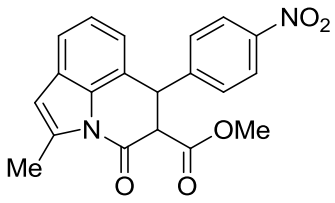


Methyl 6-(4-methoxyphenyl)-2-methyl-4-oxo-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*] quinoline-5-carboxylate (V-96a): (*Z*)-Methyl 3-(4-methoxyphenyl)-2-(2-methyl-1*H*-indole-1-carbonyl)acrylate (0.258 g, 0.739 mmol), $In(OTf)_3$ (0.0428 g, 0.0760 mmol) and 1,2-DCE (13 mL) were combined according to the general procedure to afford **V-96a** as a brown solid (0.161 g, 63%) after 3 h. (R_f 0.35, 20% EtOAc/Hex) [**m.p.** 122-124 °C] *Diastereomeric ratio*: (50:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 7.31 - 7.37 (m, 1H), 7.14 - 7.20 (m, 2H), 7.08 - 7.13 (m, 1H), 6.84 - 6.92 (m, 2H), 6.71 (d, *J* = 7.48 Hz, 1H), 6.41 (d, *J* = 1.25 Hz, 1H), 4.96 (d, *J* = 10.85 Hz, 1H), 4.19 (d, *J* = 10.88 Hz, 1H), 3.81 (s, 3H), 3.68 (s, 3H), 2.71 (d, *J* = 1.03 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 169.0, 164.0, 159.0, 137.2, 134.9, 130.9, 129.6, 127.4, 124.0, 122.7, 121.0, 118.4, 114.3, 109.4, 58.8, 55.2, 52.6, 45.3, 15.2. **IR**: 2954.7 (w), 2922.5 (w), 2850.5 (w), 1749.6 (s), 1709.3 (s), 1611.6 (w), 1513.5 (s), 1443.5 (s), 1381.8 (s), 1340.9 (s), 1252.6 (s), 1178.9 (w), 1153.2 (m), 1032.8 (m), 818.6 (m), 764.7 (m), 749.1 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 349.1314, Obs. 349.1310.



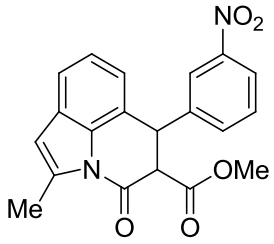
Methyl 6-(2-methoxyphenyl)-2-methyl-4-oxo-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*] quinoline-5-carboxylate (V-96b): (*Z*)-Methyl 3-(2-methoxyphenyl)-2-(2-methyl-1*H*-indole-1-carbonyl)acrylate (0.060 g, 0.172 mmol), $In(OTf)_3$ (0.0145 g, 0.0250 mmol) and toluene (4 mL) were combined according to the general procedure to afford **V-96b** as a clear oil (0.0522 g, 87%) after 3 h. (R_f 0.35, 20% EtOAc/Hex) *Diastereomeric ratio*: (3.7:1). (Trans diastereomer chemical shifts reported) **^{1}H NMR** (400 MHz, $CDCl_3$) δ

ppm 7.33 (d, *J* = 7.72 Hz, 1H), 7.23 - 7.29 (m, 1H), 7.11 (t, *J* = 7.62 Hz, 1H), 6.83 - 6.94 (m, 3H), 6.76 (d, *J* = 7.47 Hz, 1H), 6.40 (d, *J* = 1.13 Hz, 1H), 5.26 (d, *J* = 7.72 Hz, 1H), 4.41 (d, *J* = 7.65 Hz, 1H), 3.75 (s, 3H), 3.67 (s, 3H), 2.72 (d, *J* = 0.94 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 169.4, 164.4, 157.3, 137.2, 135.1, 129.7, 129.0, 127.7, 127.4, 124.0, 121.8, 120.9, 120.6, 118.1, 111.2, 109.2, 56.2, 55.4, 52.7, 41.8, 15.2. **IR**: 3065.0 (w), 3032.3 (w), 3003.1 (m), 2954.0 (m), 2839.0 (m), 1745.7 (s), 1707.2 (s), 1627.5 (w), 1600.6 (w), 1586.6 (w), 1573.3 (w), 1493.3 (m), 1443.7 (m), 1380.9 (m), 1338.7 (m), 1287.0 (m), 1210.6 (s), 1154.0 (m), 1119.0 (m), 1047.7 (w), 1026.1 (m), 967.6 (m), 911.8 (m), 820.2 (w), 748.8 (m), 732.9 (m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 349.1314, Obs. 349.1328.

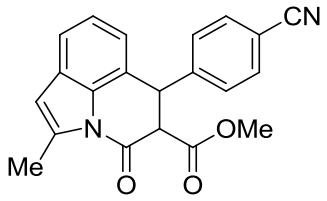


***trans*-Methyl 2-methyl-6-(4-nitrophenyl)-4-oxo-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline-5-carboxylate (V-96c):** (*Z*)-Methyl 2-(2-methyl-1*H*-indole-1-carbonyl)-3-(4-nitrophenyl)acrylate (0.070 g, 0.1922 mmol), $In(OTf)_3$ (0.0162 g, 0.0288 mmol) and toluene (4 mL) were combined according to the general procedure to afford **V-96c** as an orange oil (0.0548 g, 78.34) after 14 h. (R_f 0.40, 20% EtOAc/Hex). *Diastereomeric ratio*: (2.4:1) (Trans diastereomer chemical shifts reported) **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 8.19 - 8.28 (m, 2H), 7.42 - 7.50 (m, 2H), 7.39 (d, *J* = 7.77 Hz, 1H), 7.15 (t, *J* = 7.64 Hz, 1H), 6.64 (d, *J* = 7.48 Hz, 1H), 6.45 (d, *J* = 1.21 Hz, 1H), 5.16 (d, *J* = 10.44 Hz, 1H), 4.21 (d, *J* = 10.44 Hz, 1H), 3.69 (s, 3H), 2.71 (d, *J* = 1.17 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 168.4, 163.0, 147.6, 146.8, 137.6, 129.6, 127.8, 124.3, 124.2, 120.8, 120.6,

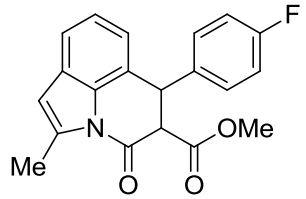
119.2, 109.6, 58.0, 53.0, 45.8, 15.2. **IR**: 3066.3 (w), 2955.2 (w), 2923.9 (w), 2850.9 (w), 1746.1 (s), 1709.3 (s), 1606.7 (w), 1519.4 (s), 1444.4 (s), 1381.0 (s), 1345.7 (s), 1285.8 (m), 1268.1 (m), 1211.2 (w), 1154.5 (s), 1109.6 (w), 1048.0 (w), 1008.1(w), 967.4 (w), 863.3 (m), 819.5 (m), 748.9 (s), 735.0 (s), 706.7 (m), 611.3 (w) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 364.1059, Obs. 364.1048.



Methyl 2-methyl-6-(3-nitrophenyl)-4-oxo-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline-5-carboxylate (V-96d): (*Z*)-Methyl 2-(2-methyl-1*H*-indole-1-carbonyl)-3-(3-nitrophenyl)acrylate (0.100 g, 0.275 mmol), $In(OTf)_3$ (0.0231 g, 0.0411 mmol) and 1,2-DCE (4 mL) were combined according to the general procedure to afford **V-96d** as a off-white solid (0.0861 g, 86%) after 13 h. (R_f 0.35, 20% EtOAc/Hex) [**m.p.** 106-108 °C] *Diastereomeric ratio*: (2.2:1). (*Trans* diastereomer chemical shifts reported) **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 8.19 - 8.28 (m, 2H), 7.42 - 7.50 (m, 2H), 7.39 (d, *J* = 7.77 Hz, 1H), 7.15 (t, *J* = 7.64 Hz, 1H), 6.64 (d, *J* = 7.48 Hz, 1H), 6.43 - 6.46 (m, 1H), 5.16 (d, *J* = 10.44 Hz, 1H), 4.21 (d, *J* = 10.44 Hz, 1H), 3.69 (s, 3H), 2.71 (d, *J* = 1.17 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 168.4, 163.0, 147.6, 146.8, 137.6, 129.6, 127.8, 125.0, 124.3, 124.2, 120.8, 120.6, 119.2, 109.6, 58.0, 53.0, 45.8, 15.2. **IR**: 3066.6 (w), 2955.3 (w), 2923.4 (w), 1746.0 (s), 1708.6 (s), 1530.3 (s), 1444.0 (s), 1380.6 (s), 1346.0 (s), 1286.5 (m), 1267.1 (m), 1154.2 (s), 1052.1 (w), 1003.0 (w), 966.4 (w), 904.1 (w), 817.3 (m), 738.9 (s), 709.5 (m), 613.4 (m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 364.1059, Obs. 364.1055.

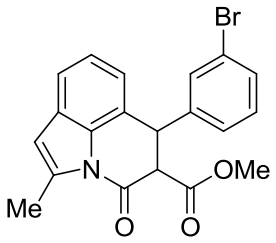


Methyl 6-(4-cyanophenyl)-2-methyl-4-oxo-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*] quinoline-5-carboxylate (V-96e): (*Z*)-Methyl 3-(4-cyanophenyl)-2-(2-methyl-1*H*-indole-1-carbonyl)acrylate (0.0900 g, 0.263 mmol), $In(OTf)_3$ (0.0220 g, 0.0392 mmol) and 1,2-DCE (4 mL) were combined according to the general procedure to afford **V-96e** as a pale orange solid (0.0704 g, 78%) after 14 h. (R_f 0.35, 20% EtOAc/Hex). [**m.p.** 155-157 °C] *Diastereomeric ratio*: (1.85:1). (*Trans* diastereomer chemical shifts reported) **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 7.66 (d, *J* = 8.25 Hz, 2H), 7.38 (d, *J* = 7.88 Hz, 3H), 7.14 (t, *J* = 7.62 Hz, 1H), 6.64 (d, *J* = 7.44 Hz, 1H), 6.44 (d, *J* = 0.92 Hz, 1H), 5.09 (d, *J* = 10.30 Hz, 1H), 4.18 (d, *J* = 10.30 Hz, 1H), 3.69 (s, 3H), 2.71 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 168.4, 163.1, 144.8, 137.5, 132.8, 129.4, 127.7, 124.3, 120.8, 120.6, 119.1, 118.4, 112.0, 109.6, 58.0, 52.9, 46.0, 15.2. **IR**: 2955.3 (w), 2922.9 (w), 2229.2 (w), 1748.4 (s), 1712.4 (s), 1532.6 (w), 1445.2 (s), 1383.0 (s), 1344.2 (m), 1275.0 (s), 1262.2 (s), 1156.3 (m), 819.0 (w), 749.7 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 344.1161, Obs. 344.1172.



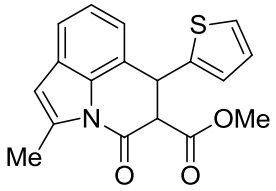
Methyl 6-(4-fluorophenyl)-2-methyl-4-oxo-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*] quinoline-5-carboxylate (V-96f): (*Z*)-Methyl 3-(4-fluorophenyl)-2-(2-methyl-1*H*-indole-1-carbonyl)acrylate (0.0760 g, 0.225 mmol), $In(OTf)_3$ (0.0188 g, 0.0330 mmol)

and 1,2-DCE (8 mL) were combined according to the general procedure to afford **V-96f** as a yellow solid (0.0716 g, 94%) after 1 h. (R_f 0.68, 30% EtOAc/Hex) [**m.p.** 153-155 °C] *Diastereomeric ratio*: (2.6:1) (*Trans* diastereomer chemical shifts reported) **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 7.36 (d, *J* = 7.77 Hz, 1H), 7.19 - 7.25 (m, 2H), 7.13 (t, *J* = 7.62 Hz, 1H), 7.00 - 7.09 (m, 2H), 6.68 (d, *J* = 7.44 Hz, 1H), 6.42 (d, *J* = 1.17 Hz, 1H), 5.01 (d, *J* = 10.85 Hz, 1H), 4.18 (d, *J* = 10.85 Hz, 1H), 3.68 (s, 3H), 2.71 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 168.8, 163.7, 137.3, 134.8, 130.2 and 130.1 (doublet), 127.5, 124.2, 122.1, 120.9, 118.7, 116.1, 115.8, 109.5, 77.2, 58.7, 52.7, 45.4, 15.2. **IR**: 3058.4 (w), 2954.5 (w), 2923.0 (w), 1746.8 (s), 1708.7 (s), 1605.3 (w), 1509.8 (s), 1443.8 (s), 1380.9 (s), 1340.0 (s), 1267.9 (m), 1224.3 (s), 1159.1 (s), 1097.6 (w), 1051.5 (w), 1010.0 (w), 967.1 (w), 818.5 (m), 748.7 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 337.1114, Obs. 337.1115.

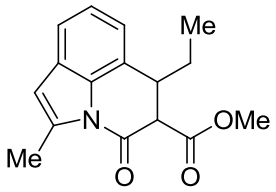


Methyl 6-(3-bromophenyl)-2-methyl-4-oxo-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*] quinoline-5-carboxylate (V-96g): (*Z*)-Methyl 3-(3-bromophenyl)-2-(2-methyl-1*H*-indole-1-carbonyl)acrylate (0.100 g, 0.252 mmol), $In(OTf)_3$ (0.0213 g, 0.0377 mmol) and 1,2-DCE (4 mL) were combined according to the general procedure to afford **V-96g** as a pale yellow solid (0.0614 g, 61%) after 14 h. (R_f 0.40, 20% EtOAc/Hex) [**m.p.** 123-125 °C] *Diastereomeric ratio*: (8.3:1). (*Trans* diastereomer chemical shifts reported) **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 7.41 - 7.49 (m, 2H), 7.33 - 7.39 (m, 1H), 7.10 - 7.27 (m, 3H), 6.69 (d, *J* = 7.48 Hz, 1H), 6.43 (d, *J* = 0.92 Hz, 1H), 4.98 (d, *J* = 10.59 Hz, 1H), 4.19

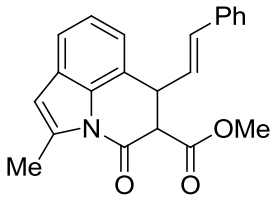
(d, *J* = 10.63 Hz, 1H), 3.70 (s, 3H), 2.71 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 168.7, 163.4, 141.6, 137.3, 134.8, 131.5, 131.1, 130.5, 127.5, 127.2, 124.2, 122.9, 121.4, 120.9, 118.8, 109.5, 58.3, 52.8, 45.7, 15.2. **IR**: 2961.7 (w), 2921.4 (w), 1750.2 (s), 1711.7 (s), 1570.7 (w), 1474.8 (w), 1444.8 (s), 1381.9 (s), 1341.5 (s), 1275.8 (s), 1261.6 (m), 1155.6 (m), 764.3 (s), 749.7 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 397.0314, Obs. 397.0315.



***trans*-Methyl 2-methyl-4-oxo-6-(thiophen-2-yl)-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*] quinoline-5-carboxylate (V-96h):** (*Z*)-Methyl 2-(2-methyl-1*H*-indole-1-carbonyl)-3-(thiophen-2-yl)acrylate (0.0900 g, 0.277 mmol), $In(OTf)_3$ (0.0233 g, 0.0415 mmol) and 1,2-DCE (4 mL) were combined according to the general procedure to afford **V-96h** as a off-white solid (0.0459 g, 51%) after 14 h. (R_f 0.40, 20% EtOAc/Hex) [**m.p.** 153-155 °C] (*Single Diastereomer*) **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 7.37 (d, *J* = 7.70 Hz, 1H), 7.23 - 7.28 (m, 1H), 7.17 (t, *J* = 7.62 Hz, 1H), 6.91 - 6.99 (m, 3H), 6.42 (s, 1H), 5.32 (d, *J* = 9.45 Hz, 1H), 4.25 (d, *J* = 9.45 Hz, 1H), 3.72 (s, 3H), 2.70 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 169.0, 163.8, 142.6, 137.8, 134.8, 128.0, 127.4, 127.0, 125.7, 124.6, 122.2, 121.3, 119.4, 109.9, 59.7, 53.3, 41.7, 15.6. **IR**: 2961.2 (w), 2927.0 (w), 1751.0 (s), 1712.1 (s), 1445.7 (s), 1382.5 (s), 1341.1 (s), 1275.5 (s), 1267.3 (m), 1156.4 (m), 1042.5 (w), 1004.0 (w), 748.9 (s), 702.5 (w) cm^{-1}**. HRMS (ESI)** M/Z+ Calc. 325.0773, Obs. 325.0754.

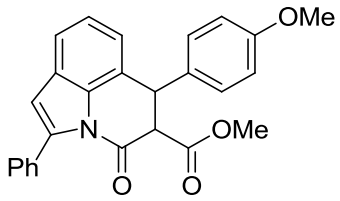


Methyl 6-ethyl-2-methyl-4-oxo-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline-5-carboxylate (V-96i): (*Z*)-Methyl 2-(2-methyl-1*H*-indole-1-carbonyl)pent-2-enoate (0.090 g, 0.332 mmol), $In(OTf)_3$ (0.0559 g, 0.0995 mmol) and toluene (5 mL) were combined according to the general procedure to afford **V-96i** as a clear oil (0.0754 g, 84%) after 12 h. (R_f 0.40, 20% EtOAc/Hex) [**m.p.** 108-110 °C] *Diastereomeric ratio*: (25:1). (*Trans* diastereomer chemical shifts reported) **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 7.33 (d, *J* = 7.48 Hz, 1H), 7.18 (t, *J* = 7.55 Hz, 1H), 7.06 (d, *J* = 6.00 Hz, 1H), 6.35 - 6.39 (m, 1H), 3.86 (d, *J* = 4.69 Hz, 1H), 3.61 - 3.71 (m, 4H), 2.66 - 2.73 (m, 3H), 1.78 - 1.95 (m, 1H), 1.61 - 1.77 (m, 1H), 0.95 (t, *J* = 7.40 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 169.6, 164.3, 136.9, 134.6, 127.5, 123.7, 121.7, 120.6, 118.1, 109.2, 55.8, 52.8, 41.5, 27.2, 15.1, 10.6. **IR**: 2963.1 (w), 2927.6 (w) 1743.0 (w), 1715.0 (s), 1629.2 (s),1573.2 (w), 1447.6 (w), 1381.4 (s), 1328.6 (m), 1274.9 (m), 1259.8 (m), 1194.6 (w), 1160.3 (w), 821.1 (w), 763.4 (m), 750.0 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 271.1208, Obs. 271.1208.



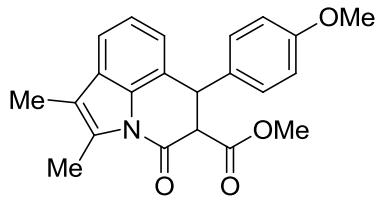
(*E*)-methyl 2-methyl-4-oxo-6-styryl-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline-5-carboxylate (V-96j): (2*Z*, 4*E*)-Methyl 2-(2-methyl-1*H*-indole-1-carbonyl)-5-phenylpenta-2,4-dienoate (0.0700 g, 0.203 mmol), $In(OTf)_3$ (0.0341 g, 0.0608 mmol) and

toluene (4 mL) were combined according to the general procedure to afford **V-96j** as a pale yellow solid (0.0457 g, 65%) after 14 h. (R_f 0.35, 20% EtOAc/Hex) [**m.p.** 98-100 °C] *Diastereomeric ratio*: (20:1). (*Trans* diastereomer chemical shifts reported) **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 7.26 - 7.43 (m, 6H), 7.21 (t, *J* = 7.57 Hz, 1H), 7.08 (d, *J* = 7.40 Hz, 1H), 6.63 (d, *J* = 15.68 Hz, 1H), 6.40 (d, *J* = 1.14 Hz, 1H), 6.24 (dd, *J* = 8.65, 15.68 Hz, 1H), 4.58 (t, *J* = 9.44 Hz, 1H), 4.00 (d, *J* = 10.22 Hz, 1H), 3.78 (s, 3H), 2.70 (d, *J* = 1.10 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 169.0, 164.0, 137.2, 136.2, 134.6, 134.5, 128.6, 128.0, 127.6, 126.5, 126.4, 124.1, 121.0, 120.5, 118.8, 109.3, 56.7, 52.8, 43.9, 15.2. **IR**: 3026.9 (w), 2952.8 (w), 2922.4 (w), 1749.6 (s), 1709.8 (s), 1444.3 (s), 1380.9 (s), 1340.2 (m), 1276.0 (m), 1260.8 (m), 1200.1 (w), 1151.3 (m), 968.1 (w), 813.1 (w), 749.0 (s), 695.0 (m)cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 345.1365, Obs. 345.1360.



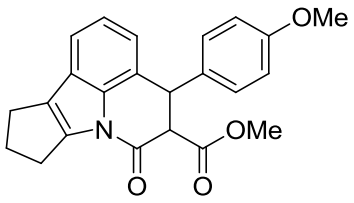
Methyl 6-(4-methoxyphenyl)-4-oxo-2-phenyl-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*] quinoline-5-carboxylate (V-96k): (*Z*)-Methyl 3-(4-methoxyphenyl)-2-(2-phenyl-1*H*-indole-1-carbonyl)acrylate (0.160 g, 0.390 mmol), $In(OTf)_3$ (0.0223 g, 0.0400 mmol) and 1,2-DCE (13 mL) were combined according to the general procedure to afford **V-96k** as a reddish orange solid (0.155 g, 97%) after 3 h. (R_f 0.33, 20% EtOAc/Hex) [**m.p.** 108-110 °C] *Diastereomeric ratio*: (17.3:1). (*Trans* diastereomer chemical shifts reported) **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 8.16 - 8.22 (m, 1H), 7.71 - 7.76 (m, 1H), 7.16 - 7.45 (m, 7H), 7.02 - 7.09 (m, 2H), 6.71 - 6.77 (m, 2H), 5.19 (d, *J* = 4.40 Hz, 1H), 4.05 (d, *J* = 4.43 Hz, 1H), 3.86 (s, 3H), 3.73 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 168.0, 164.9,

158.9, 139.4, 134.4, 132.0, 131.7, 130.5, 128.4, 128.4, 128.4, 127.0, 124.9, 124.5, 120.2, 116.7, 114.3, 114.1, 63.0, 55.2, 53.3, 42.7. **IR**: 3056.9 (w), 2953.2 (w), 2837.9 (w), 1730.5 (s), 1610.2 (s), 1511.9 (s), 1454.6 (s), 1392.4 (s), 1345.1 (m), 1305.2 (m), 1246.7 (s), 1145.4 (s), 1103.0 (w), 1029.6 (s), 830.8 (m), 748.6 (s), 699.8 (s), 628.6 (m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 411.1471, Obs. 411.1470.

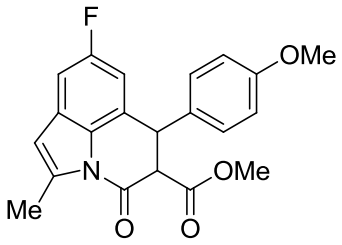


Methyl 6-(4-methoxyphenyl)-1,2-dimethyl-4-oxo-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*] quinoline-5-carboxylate (V-96l): (*Z*)-Methyl 2-(2,3-dimethyl-1*H*-indole-1-carbonyl)-3-(4-methoxyphenyl)acrylate (0.0900 g, 0.2476 mmol), $In(OTf)_3$ (0.0208 g, 0.0371 mmol) and DCE (5 mL) were combined according to the general procedure to afford **V-96l** as a clear oil (0.7740 g, 86%) after 4 h. R_f 0.40 (20% EtOAc/Hex). *Diastereomeric ratio*: (50:1). (*Trans* diastereomer chemical shifts reported) **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.31 (d, *J* = 7.72 Hz, 1H), 7.12 - 7.19 (m, 3H), 6.85 - 6.89 (m, 2H), 6.72 (d, *J* = 7.47 Hz, 1H), 4.94 (d, *J* = 10.60 Hz, 1H), 4.17 (d, *J* = 10.60 Hz, 1H), 3.81 (s, 3H), 3.68 (s, 3H), 2.64 (d, *J* = 0.82 Hz, 3H), 2.22 (d, *J* = 0.88 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 169.2, 163.6, 159.0, 134.0, 132.3, 131.2, 129.5, 129.1, 123.9, 122.5, 121.1, 116.9, 116.7, 114.3, 58.9, 55.2, 52.6, 45.2, 12.4, 8.6. **IR**: 3035.9 (w), 2999.5 (w), 2953.5 (m), 2924.2 (m), 2837.8 (m), 1747.0 (s), 1700.9 (s), 1627.9 (w), 1610.8 (m), 1585.2 (w), 1512.4 (s), 1452.4 (s), 1378.4 (s), 1353.9 (s), 1338.2 (s), 1286.7 (m), 1250.0 (s), 1211.6 (m), 1178.1 (m), 1155.5 (s), 1136.1 (w), 1112.2 (w), 1030.9 (m), 980.7 (w), 912.6 (w), 850.7 (w),

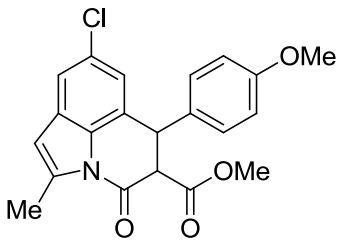
822.5 (w), 792.4 (w), 768.1 (w), 746.4 (m), 731.9 (m), 610.7 (w) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 363.1471, Obs. 363.1465.



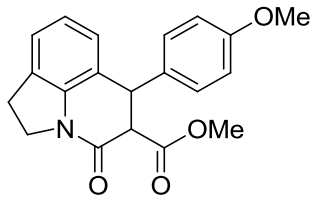
***trans*-Methyl 4-(4-methoxyphenyl)-6-oxo-4,5,6,8,9,10-hexahydrocyclopenta[4,5] pyrrolo[3,2,1-*ij*]quinoline-5-carboxylate (V-96m):** (*Z*)-Methyl 3-(4-methoxyphenyl)-2-(1,2,3,4-tetrahydrocyclopenta[*b*]indole-4-carbonyl)acrylate (0.0450 g, 0.120 mmol), $In(OTf)_3$ (0.0101 g, 0.0178 mmol) and toluene (3 mL) were combined according to the general procedure to afford **V-96m** as a white solid (0.0369 g, 82%) after 12 h. (R_f 0.40, 20% EtOAc/Hex) [**m.p.** 140-142 °C] (*Single Diastereomer observed*) **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 7.39 - 7.47 (m, 2H), 7.13 - 7.29 (m, 2H), 7.03 - 7.09 (m, 1H), 6.76 - 6.82 (m, 2H), 3.91 (s, 1H), 3.89 (d, *J* = 0.40 Hz, 3H), 3.75 (s, 3H), 3.74 (s, 1H), 2.49 (td, *J* = 5.46, 13.07 Hz, 1H), 2.29 - 2.41 (m, 1H), 2.03 - 2.27 (m, 2H), 1.75 - 1.87 (m, 2H). **^{13}C NMR** (75 MHz, CHLOROFORM-*d*) δ ppm 170.4, 169.2, 160.6, 147.1, 141.0, 140.0, 133.9, 128.1, 126.3, 125.9, 123.3, 117.4, 114.6, 109.6, 91.5, 67.9, 59.9, 55.5, 53.0, 51.7, 37.7, 36.3, 26.3. **IR**: 3059.4 (w), 2953.0 (w), 2867.2 (w), 1737.7 (s), 1708.1 (s), 1601.1 (m), 1579.5 (w), 1487.4 (m), 1474.2 (m), 1480.2 (m), 1352.9 (m), 1331.6 (m), 1304.1 (m), 1272.9 (s), 1227.6 (s), 1174.0 (m), 1156.2 (m), 1111.4 (w), 1096.0 (w), 1029.9 (s), 863.2 (w), 844.6 (w), 821.6 (w), 752.2 (s), 734.8 (s), 712.7 (m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 375.1471, Obs. 375.1476.



***trans*-Methyl 8-fluoro-6-(4-methoxyphenyl)-2-methyl-4-oxo-5,6-dihydro-4*H*-pyrrolo [3,2,1-*ij*]quinoline-5-carboxylate (V-96n):** (*Z*)-Methyl 2-(5-fluoro-2-methyl-1*H*-indole-1-carbonyl)-3-(4-methoxyphenyl)acrylate (0.0750 g, 0.204 mmol), $In(OTf)_3$ (0.0180 g, 0.0320 mmol) and 1,2-DCE (7 mL) were combined according to the general procedure to afford **V-96n** as a yellow solid (0.660 g, 88%) after 12 h. (R_f 0.40, 20% EtOAc/Hex) [**m.p.** 106-108 °C] *(Single Diastereomer Observed)* **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.13 - 7.18 (m, 2H), 7.01 (ddd, *J* = 0.63, 2.21, 8.96 Hz, 1H), 6.86 - 6.91 (m, 2H), 6.43 - 6.48 (m, 1H), 6.37 - 6.39 (m, 1H), 4.92 (d, *J* = 10.79 Hz, 1H), 4.17 (d, *J* = 10.85 Hz, 1H), 3.81 (s, 3H), 3.68 (s, 3H), 2.70 (d, *J* = 1.19 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 168.8, 163.7, 161.7, 159.3, 159.2, 138.7, 131.1, 130.3, 129.5, 128.1 and 128.0 (d), 124.0 and 123.9 (d), 114.4, 109.2, 109.2, 109.1, 108.9, 104.7, 104.4, 58.5, 55.2, 52.7, 45.3, 15.2. **IR**: 3001.9 (w), 2954.8 (w), 2838.9 (w), 1747.3 (s), 1709.5 (s), 1632.7 (m), 1610.7 (m), 1513.3 (s), 1479.6 (s), 1435.4 (s), 1381.4 (s), 1327.8 (m), 1254.6 (s), 1210.5 (s), 1156.7 (s), 1112.8 (s), 1031.8 (s), 961.2 (m), 852.7 (s), 832.2 (s), 741.1 (s), 714.0 (m), 619.6 (m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 367.1220, Obs. 367.1227.

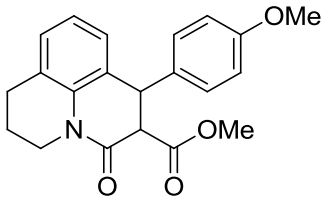


Methyl 8-chloro-6-(4-methoxyphenyl)-2-methyl-4-oxo-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline-5-carboxylate (V-96o): (*Z*)-Methyl 2-(5-chloro-2-methyl-1*H*-indole-1-carbonyl)-3-(4-methoxyphenyl)acrylate (0.0100 g, 0.261 mmol), $In(OTf)_3$ (0.0220 g, 0.0391 mmol) and toluene (5 mL) were combined according to the general procedure to afford **V-96o** as a white solid (0.0900 g, 90%) after 4 h. (R_f 0.45, 20% EtOAc/Hex) [**m.p.** 132-134 °C] *Diastereomeric ratio*: (100:1) (*Trans* diastereomer chemical shifts reported) **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 7.29 - 7.33 (m, 1H), 7.11 - 7.18 (m, 2H), 6.85 - 6.93 (m, 2H), 6.68 (d, *J* = 1.10 Hz, 1H), 6.35 (d, *J* = 1.14 Hz, 1H), 4.91 (d, *J* = 10.74 Hz, 1H), 4.16 (d, *J* = 10.77 Hz, 1H), 3.81 (s, 3H), 3.67 (s, 3H), 2.69 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 168.6, 163.7, 159.2, 138.5, 133.2, 130.1, 129.7, 129.5, 128.4, 123.9, 121.1, 118.3, 114.4, 108.6, 58.5, 55.2, 52.7, 45.2, 15.2. **IR** 2954.9 (w), 2838.0 (w), 1747.7 (s), 1710.5 (s), 1611.3 (m), 1513.0 (s) 1462.4 (m), 1427.7 (m), 1371.8 (s), 1251.1 (s), 1210.2 (m), 1178.1 (m), 1152.2 (s), 1031.1 (m), 886.2 (m), 858.6 (m), 829.4 (m), 763.7 (w), 737.9 (s), 701.6 (m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 383.0924, Obs. 383.0923.



Methyl 6-(4-methoxyphenyl)-4-oxo-2,4,5,6-tetrahydro-1*H*-pyrrolo[3,2,1-*ij*]quinoline-5-carboxylate (V-98): (*Z*)-Methyl 2-(indoline-1-carbonyl)-3-(4-methoxyphenyl)acrylate (0.0750 g, 0.222 mmol), $In(OTf)_3$ (0.0187 g, 0.0333 mmol) and toluene (5 mL) were combined according to the general procedure to afford **V-98** as a off-white solid (0.0606 g, 81%) after 42 h. (R*f* 0.40, 20% EtOAc/Hex) [**m.p.** 69-71 °C] (Mixture of *Single Diastereomer and Decarboxylated product*) **^{1}H NMR** (300 MHz, $CDCl_3$) δ ppm 7.06 -

7.17 (m, 7.16), 6.84 - 6.93 (m, 7.14), 6.64 - 6.75 (m, 2.38), 4.66 (d, *J* = 10.77 Hz, 1.00), 4.27 (dd, *J* = 7.05, 9.69 Hz, 1.36), 4.02 - 4.22 (m, 5.13), 3.77 - 3.87 (m, 8.16), 3.65 (s, 3.16), 3.17 - 3.33 (m, 5.05), 2.77 - 2.98 (m, 2.87). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 169.7, 166.9, 162.9, 158.9, 158.6, 141.0, 140.1, 133.7, 131.2, 129.3, 128.9, 128.8, 125.6, 125.4, 124.0, 123.9, 123.6, 123.5, 122.6, 114.3, 114.2, 57.0, 55.2, 55.2, 52.5, 45.5, 45.2, 45.0, 41.4, 40.2, 27.9. **IR**: 3035.8 (w), 2951.3 (w), 2837.7 (w), 1745.8 (m), 1668.2 (s), 1595.3 (m), 1512.9 (s), 1480.9(s), 1468.7 (m), 1396.6 (m), 1353.3 (w), 1250.1 (s), 1178.6 (w), 1153.9 (w), 1031.8 (w), 834.7 (w), 764.9 (m), 747.5 (m) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 337.1314, Obs. 337.1313.



***trans*-Methyl 4-(4-methoxyphenyl)-3-oxo-1,2,3,5,6,7-hexahydropyrido[3,2,1-*ij*] quinoline-2-carboxylate (V-99):** (*Z*)-Methyl 3-(4-methoxyphenyl)-2-(1,2,3,4-tetrahydroquinoline-1-carbonyl)acrylate (0.075 g, 0.213 mmol), $In(OTf)_3$ (0.0179 g, 0.0320 mmol) and toluene (5 mL) were combined according to the general procedure to afford **V-99** as a colorless oil (0.0622 g, 83%) after 42 h. (R_f 0.40, 20% EtOAc/Hex) (*Single Diastereomer observed*) **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.07 - 7.12 (m, 2H), 7.02 - 7.06 (m, 1H), 6.83 - 6.91 (m, 3H), 6.65 - 6.69 (m, 1H), 4.53 (d, *J* = 10.04 Hz, 1H), 3.96 - 4.04 (m, 1H), 3.82 - 3.91 (m, 2H), 3.79 (s, 3H), 3.62 (s, 3H), 2.85 (t, *J* = 6.27 Hz, 2H), 1.93 - 2.03 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ ppm 169.3, 165.0, 158.8, 134.9, 131.0, 129.3, 128.5, 127.1, 126.4, 125.4, 123.0, 114.3, 55.2, 55.0, 52.5, 43.9, 41.3, 27.3, 21.3. **IR**: 3003.2 (w), 2950.0 (w), 2886.7 (w), 1746.6 (s), 1666.8 (s), 1612.8 (w), 1592.4

(w), 1513.7 (s), 1469.9 (m), 1460.9 (w), 1383.3 (m), 1274.9 (m), 1251.2 (m), 1179.0 (w), 1154.0 (w), 1031.7 (w), 764.4 (s), 749.9 (s) cm^{-1}. **HRMS (ESI)** M/Z+ Calc. 351.1471, Obs. 351.1477.

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CHAPTER 6

DIASTEREOSELECTIVE SYNTHESIS OF (±)-DEETHYLEBURNAMONINE[‡‡]

6.1. INTRODUCTION TO *VINCA-EBURNA* AND *TACAMAN* NATURAL PRODUCTS

The *vinca-eburna*[1] and the structurally-related *tacaman*[2] families of indole alkaloids occupy a central place in natural product chemistry due to their wide range of complex structural variation. It also represents a large group of biologically-active, naturally-occurring indole alkaloids that are isolated from several plants of the *Apocyanaceae* and *Tabernaemontana* genera. These biogenetically related *vinca-eburnan* and *tacaman* families is characterized by a common pentacyclic framework (**VI-1**) that contains either a *cis*- or *trans*-fused D/E ring system (Figure 6.1).[3] The *eburnan* skeleton has an ethyl group at C*(20)*, while the *tacaman* skeleton has the ethyl group at C*(14)* instead,[4] and include eburnamine **VI-2,** eburnamonine **VI-3**, vincamine **VI-4**, vinpocetine **VI-5**, deethyleburnamonine **VI-6**, vindeburnol **VI-8**, criocerine **VI-9**, strempeliopine **VI-10**, tacamonine **VI-11**, tacamine **VI-12**, and avotacamine **VI-13** among their prototypical members. While the vast majority of compounds belonging to these families have a *cis*-fused D/E ring system, several important biologically-active derivatives, such as vindeburnol **VI-8**, possess a *trans*-fused junction.

[‡‡]This work was performed in collaboration with Marchello A. Cavitt, a fellow graduate student in the France research group.

Many of these compounds exhibit a variety of pharmacological activities, ranging from antitumor activity to muscle-stimulating activity.[5] Over the past 10 years, numerous efforts to fully understand the compounds' modulatory effects on brain circulation and neuronal homeostasis have been reported.[6] For example, vincamine **VI-4** has been shown to have neuroprotective effects resulting from the blockage of voltage-gated sodium ion channels.[7] Similarly, vinpocetine (**VI-5)**, the most extensively studied cogener of the *eburnan* class, is currently prescribed in Europe (*tradename*: Cavinton) for the treatment of disorders arising from cerebrovascular and cerebral neurodegenerative diseases.[8] This therapeutic potential has led to intense pharmacological and synthetic studies over the past several decades.[9]

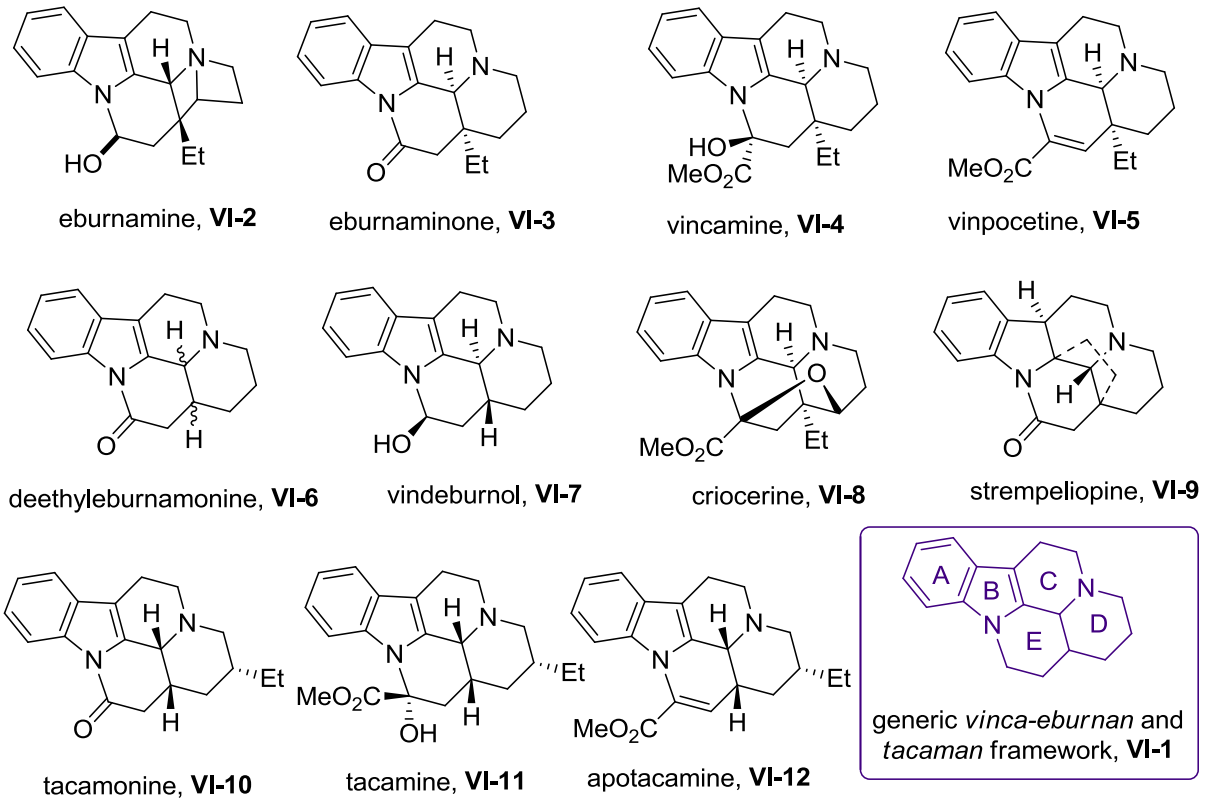


Figure 6.1. Representative *Vinca-Eburna* and Tacaman Indole Alkaloids

6.2. SYNTHETIC STUDIES ON (±)-DEETHYLEBURNAMONINE

Several synthetic strategies have been reported for the assembly of the pentacyclic core present in the natural products and their analogues. The most common approach is to establish the [ABCD]-type octahydroindolo[2,3-*a*]-quinolizine ring skeleton starting from suitable indole precursor and subsequent formation of the E-ring as desired in the final target. The ABCD ring system is most often prepared by one of the following methods: (1) a Pictet-Spengler/Bischler-Napieralski cyclization;[10] (2) a Michael-type annulation;[11] or (3) annulation reactions of dihydro-*β*-carboline derivatives.[12] In 2008, Padwa and co-workers published an alternate route to the *eburna-vinca* and *tacaman* alkaloids that involves a Rh(II)-catalyzed intramolecular dipolar cycloaddition of an α-diazo indoloamide, followed by reductive ring-opening and base-induced keto-amide ring contraction to build the full ABCDE skeleton.[13] The remaining part of this section will provide a brief synopsis of approaches towards the synthesis of (±)-deethyleburnamonine.

6.2.1. <u>POTIER'S APPROACH</u>

The Potier group disclosed the first synthesis of (±)-deethyleburnamonine in 1973 using a reductive cyclization of a pyridinium salt in the presence of hydrogen.[14] The pyridinium salt **VI-13** obtained from tryptophyl bromide and methyl nicotinate. The hydrogenation of an ethanolic solution of **VI-13** over PtO_2 at room temperature yielded **VI-6b** in 15% yield along with hexahydro products **VI-14** and **VI-15** (Figure 6.2).

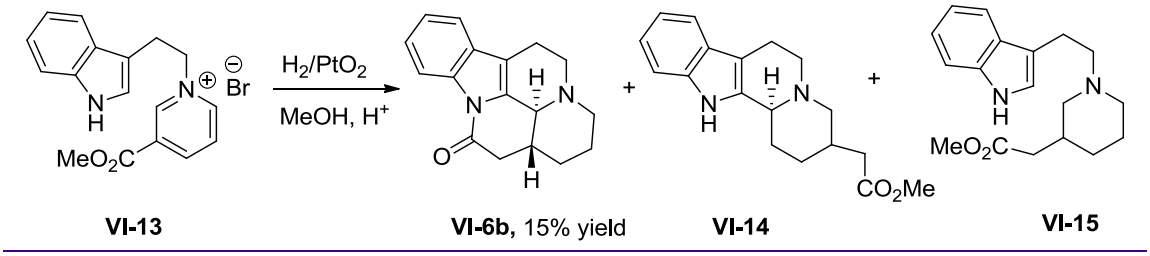


Figure 6.2. Potier's Synthesis of *trans*-Deethyleburnamonine using a Reductive Cyclization

6.2.2. LOUNASMAA'S APPROACH

In 1988, Lounasmaa reported the total synthesis of (±)-deethyleburnamonine utilizing the modified Potier-Polonovski reaction and Pictet-Spengler-type cyclization.[15] The pyridinium salt **VI-13** was efficiently transformed into *N*-Boc protected tryptophylpiperidine **VI-16** through a sequence that involved a catalytic hydrogenation over PtO_2 followed by protection of indole with *t*-butyloxycarbonyl anhydride (Figure 6.3). *N-Boc*-tryptophylpiperidine **VI-16** was converted into corresponding *N*-oxide, which was then submitted to the modified Polonovski condition, followed by cyanide trapping to furnish key intermediate *α*-aminonitrile **VI-17**. The $AgBF_4$-induced Pictet-Spengler-type cyclization of α-aminonitrile followed by a spontaneous lactamization afforded desired *trans-d*eethyleburnamonine product **VI-6b** in 70% yield.

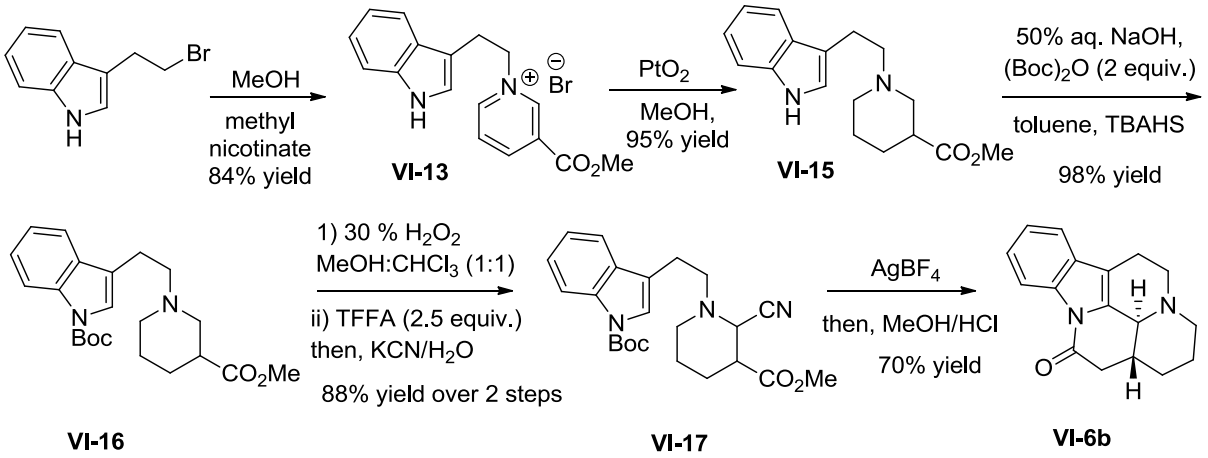


Figure 6.3. Lounasmaa's Synthesis of *trans*-Deethyleburnamonine

In continuation of their studies directed towards the synthesis of vincamine-eburnamonine derivatives, Lounasmaa and co-workers developed an efficient stereoselective acid-catalyzed epimerization of 1-substituted indolo[2,3-*a*]quinolizidines to generate *cis*- and *trans*-deethyleburnamonine starting common intermediate **VI-19** (Figure 6.4).[16] The key ester precursor **VI-19** was synthesized in three steps from tryptophyl bromide and methyl nicotinate involving Pd-catalyzed hydrogenation followed by an acid-induced cyclization. Reduction of **VI-19** with LAH gave in its corresponding alcohol **VI-20** in high yields, which was then rapidly transformed into its nitrile derivative **VI-22** via tosylate **VI-21**. Finally, mild acid treatment of **VI-22** afforded desired product **VI-6b** in 55% over two steps. Treatment of ester derivative **VI-19** with TFA under reflux furnished the other isomer, which was then converted to *cis*-deethyleburnamonine using identical homologation processes.

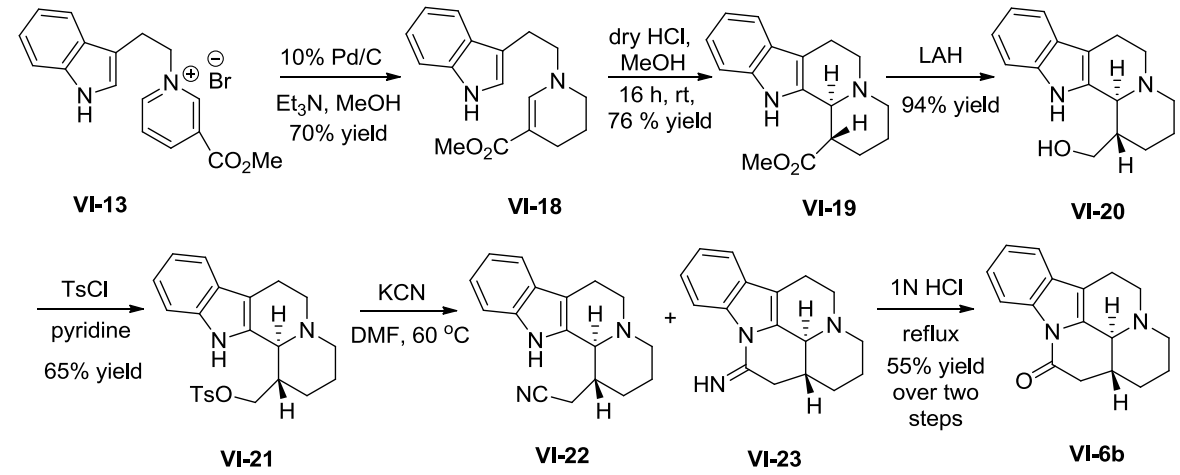


Figure 6.4. Lounasmaa's Second Generation Synthesis of *trans*-Deethyleburnamonine

In 1999, Lounasmaa reported further modification in the synthesis of deethyleburnamonine by making use of base-catalyzed cyclization of nitrile derivative **VI-22.**[17] Tetracyclic nitrile **VI-22** was heated to reflux in methanolic solution of NaOMe, and the cycle was repeated until higher conversions to imine **VI-23** were achieved. When imine **VI-23** was heated to reflux in 25% HCl, (±)-deethyleburnamonine **VI-6b** was obtained in 97% yield (Figure 6.5).

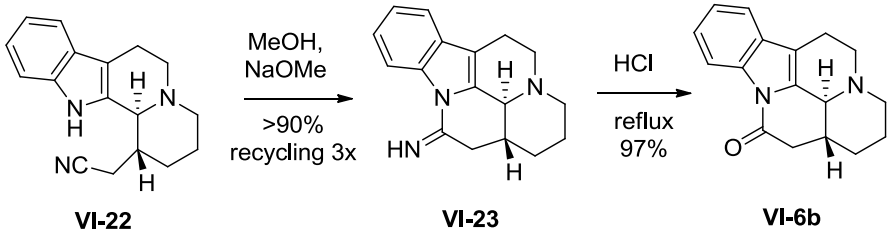


Figure 6.5. Lounasmaa's Third Generation Synthesis of *trans*-Deethyleburnamonine

6.2.3. STOIT'S APPROACH

In 1989, Stoit and Pandit disclosed the application of the substituted 5,10-methylenetetrahydrofolate model towards the formal synthesis of deethyleburnamonine.[18] Stoit generated the required substituted 5,10-methylenetetrahydrofolate model **VI-25** using the addition of the dianion of dimethyl 2-methoxycarbonylglutarate **VI-24** to 1,5,5-trimethyl-3-tosyl-l-imidazolidinium iodide (Figure 6.6). Next, 7-carbon functionalized carbon fragment transfer on tryptamine was achieved using AcOH in refluxing acetonitrile to afford mixture of *E/Z* isomers **VI-26**. Without separation, this mixture was treated with acidic conditions to furnish **VI-27** in 95% yield. The treatment of **VI-27** with AcOH/Et_3N mixture to generate diastereomeric pair of lactams **VI-28** in 75% yields. The lactam **VI-28b** upon decarbomethoxylation followed by LAH reduction provided Lounasmaa's alcohol intermediate **VI-20** and completed Stoit's formal synthesis.

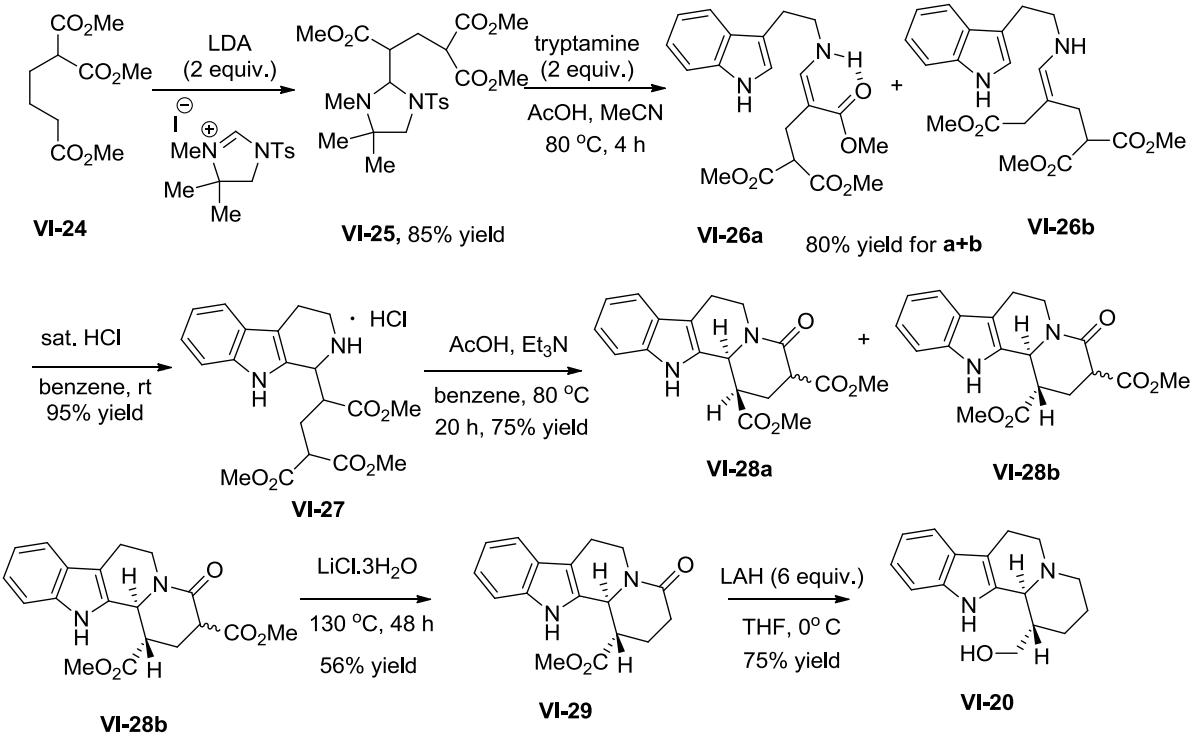


Figure 6.6. Stoit's Formal Synthesis of *trans*-Deethyleburnamonine

6.2.4. MASSIOT'S APPROACH

Massiot et al. reported the Rh(III)-catalyzed isomerization-cyclization of indolyl-tetrahydropiperidine approach for the synthesis of deethyleburnamonine.[19] The pyridinium salts V**I-13** was subjected to reduction using $NaBH_4$ to generate tetrahydropyridine key precursor **VI-30.** When ester **VI-30** was reacted in the presence of Rh(III)-salts underwent isomerization of alkene to generate enamine intermediate **VI-32a,** which immediately cyclized through a tandem fashion to furnish the pentacyclic deethyleburnamonine **VI-6b** in 23% yield (Figure 6.7).

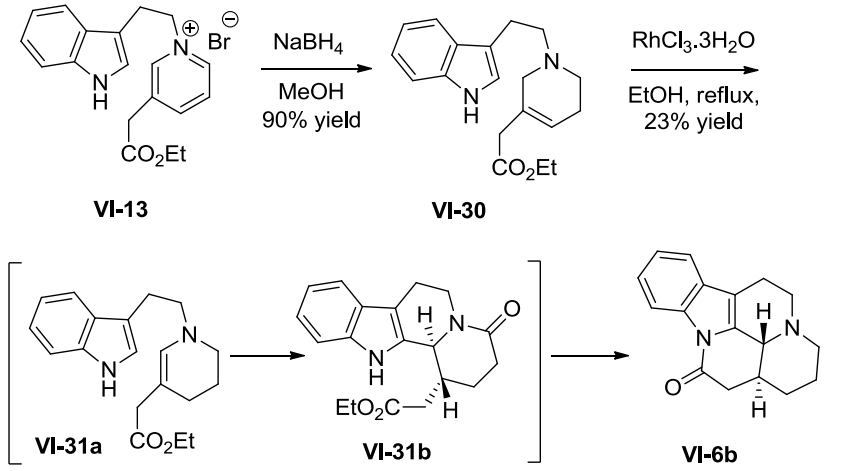


Figure 6.7. Massiot's Synthesis of *trans*-Deethyleburnamonine

6.2.5. MANN'S APPROACH

In 2011, Mann and co-workers reported an expeditious route to deethyleburnamonine, a direct precursor of vinderburnol via one-pot allylamine-enamine isomerization, followed by a rare Pictet-Spengler condensation.[20] The tetrahydropiperidine precursor **VI-30** was obtained in two steps described previously using tryptophyl bromide and ethylhomonicotinate. The allyl amine **VI-30** was then subjected to DBU and irradiated using microwave irradiation at 160^{o}C for 6 h, furnished deethyleburnamonine in 64% yield (Figure 6.8). This total synthesis represent the shortest synthesis with three steps, providing (±)-deethyleburnamonine product in 52% overall yield.

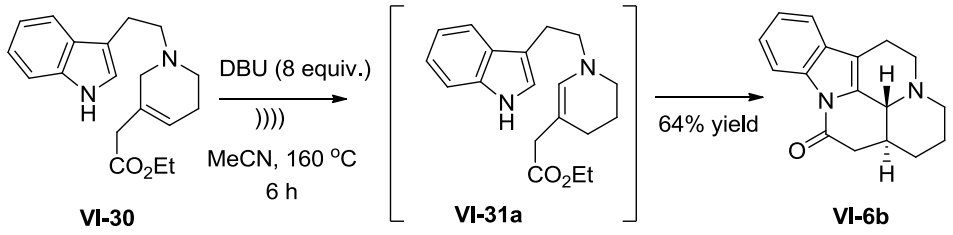


Figure 6.8. Mann's Synthesis of *trans*-Deethyleburnamonine

6.3. CYCLOPROPANE RING-OPENING/FRIEDEL-CRAFTS APPRAOCH TO (±)-DEETHYLEBURNAMONINE

Previous work in our lab demonstrated that 30 mol % $In(OTf)_3$ successfully catalyzes the cyclizations of alkenyl cyclopropyl ketones and cyclopropyl heteroaryl ketones to form the functionalized cyclohexyl rings.[21] The use of the donor-acceptor cyclopropanes bearing a secondary electron acceptor (an ester group) is essential, as it permits effective catalysis under mild reaction conditions. In continuation of our studies focusing on utilizing donor-acceptor cyclopropanes to generate interesting carbo- and heterocycles, in 2011 we disclosed our report on $In(OTf)_3$-catalyzed tandem ring-opening/intramolecular Friedel-crafts cyclization of donor-acceptor cyclopropanes for the facile construction of hydropyrido[1,2-*a*]indole derivatives in good to excellent yields (up to >99%) (Figure 6.9).[22] The methodology is highly modular, operationally simple and amenable to a diverse number of functional groups and substitution patterns. Success with this methodology, prompted us to investigate the possibility of using our methodology for the rapid construction of the pentacyclic framework of the *eburnan* and *tacaman* classes of alkaloids, both of which possess the 6,7,8,9-tetrahydropyrido[1,2-*a*]indole ring system. More specifically, we determined to choose (±)-deethyleburnamonine (**VI-6**) as an initial synthetic target because it represents the simplest example of both the alkaloid classes (no ethyl group present). Using our methodology, the ABDE rings could be rapidly accessed, in contrast to previous reports that primarily focus on initial assembly of ABCD rings.

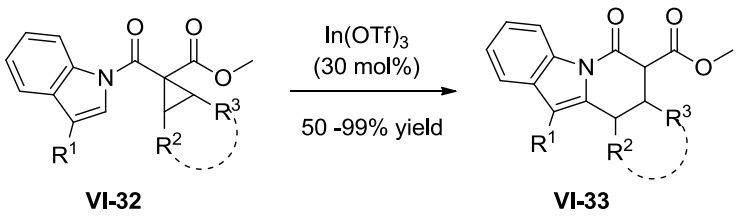


Figure 6.9. Tandem Cyclopropane Ring-Opening/F-C Alkylation Sequence

6.3.1. RETROSYNTHETIC ANALYSIS

The France group envisioned that (±)-deethyleburnamonine would arise from the ABDE tetracycle **VI-34** following *N*-deprotection, *N*-alkylation (C-ring formation), and decarbalkoxylation (Figure 6.10). Tetracycle **VI-35** would then be generated from the *N*-acylated indolyl cyclopropane **VI-36** *via* an indium-catalyzed cyclization of D-A-A cyclopropane. The requisite cyclopropane is expected to arise from the *N*-acylation, diazo transfer, and Rh-catalyzed cyclopropanation of tryptophyl bromide.

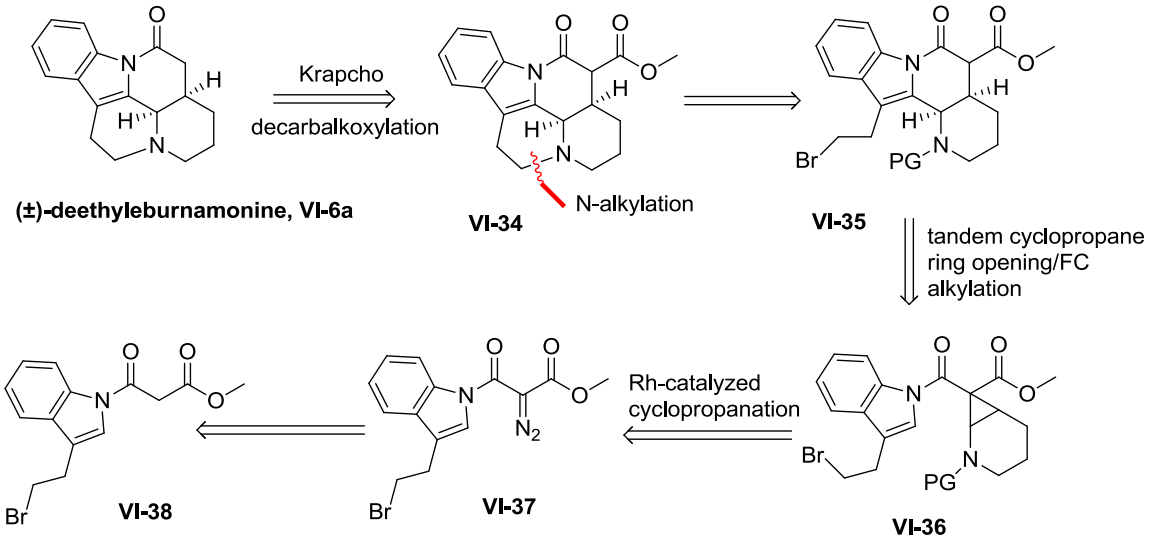


Figure 6.10. Proposed Retrosynthetic Analysis for (±)-Deethyleburnamonine

6.3.2. SYNTHESIS OF THE MODEL SUBSTRATE

Our initial analysis of the target structure led us to focus on the construction of tetracyclic hydropyrido[1,2-*a*]indole core of the molecule via our tandem cyclopropane ring-opening/F-C alkylation sequence. To achieve this, it was decided to use cyclopropyl **VI-41** derived from 3-methyl indole and Cbz-protected 3,4-dihyropyridine as our model substrate. The requisite model substrate was synthesized in three high yielding steps involving *N*-acylation, diazo transfer, and Rh-catalyzed cyclopropanation with Cbz-protected 3,4-dihydropyridine (Figure 6.11).

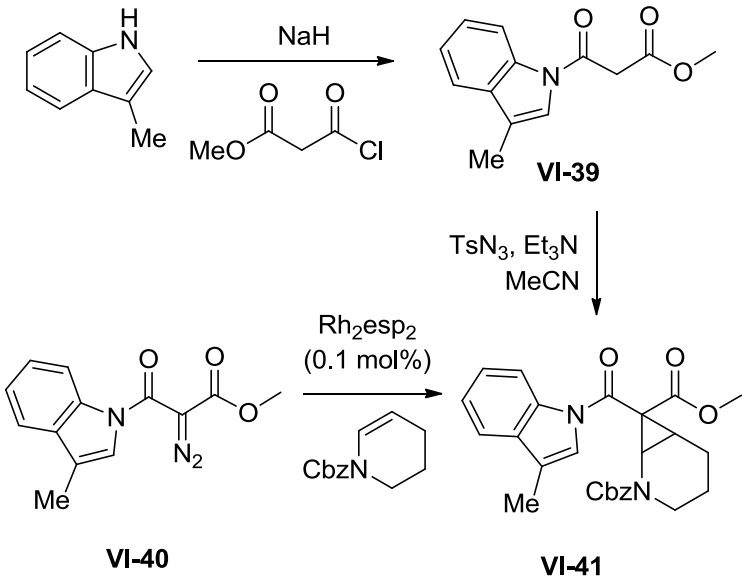


Figure 6.11. Model Substrate Synthesis

With the model substrate in hand, it was subjected to our tandem cyclopropane ring-opening/F-C alkylation reaction conditions. It readily cyclized to provide the desired tetracyclic hydropyrido[1,2-*a*]indole product in 97% yield with a 7.5:1 *dr* (Figure 6.12). This result is noteworthy as the D/E rings of the product possesses only the 20,21-*cis*-ring

junction with **VI-42** being formed with a 7.5:1 diastereomeric preference for the all-*cis* isomer.

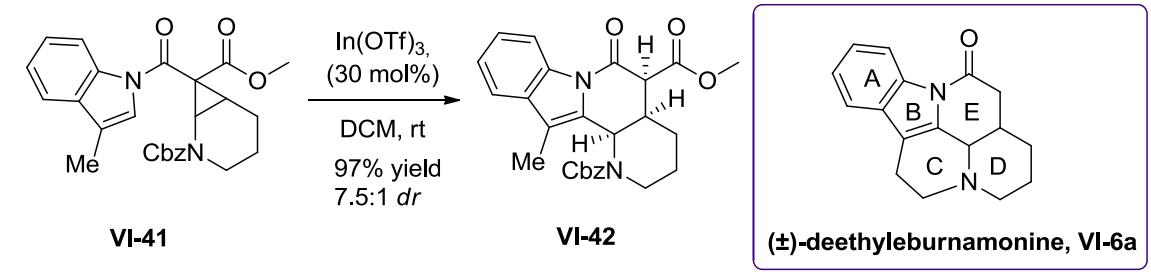


Figure 6.12. Test Reaction on Model Substrate

6.3.3. STRATEGY FOR THE SYNTHESIS OF (±)-DEETHYLEBURNAMONINE

Success of the proposed route is predicated on facile access to cyclopropane **VI-36a**, which was readily synthesized in three steps (Figure 6.13). Commercially available 3-(2-bromoethyl)-1*H*-indole was treated with methyl malonyl chloride to provide the required *β*-ester amide **VI-38** in 84% yield. Next, diazo transfer with tosyl azide provided the α-diazo ester **VI-39** in 88% yield. The resulting diazo species **VI-38** was treated with Rh_2esp_2 in the presence of the Cbz-protected 2,3-dihyropyridine afforded the requisite cyclopropane **VI-36a** in 81% yield. With a fully functionalized cyclopropyl precursor in hand, it was treated with 30 mol% $In(OTf)_3$. As anticipated, the substrate **VI-36a** readily cyclized to form tetracycle **VI-35a** in 97% yield. The major product formed was the all-*cis* diastereomer with 8:1 *dr*. With **VI-35a** in hand, we envisioned that C-ring formation (*N*-alkylation) should be facile upon Cbz-deprotection. Unfortunately, the desired product was not observed when a variety of deprotection conditions were attempted, including hydrogenation.

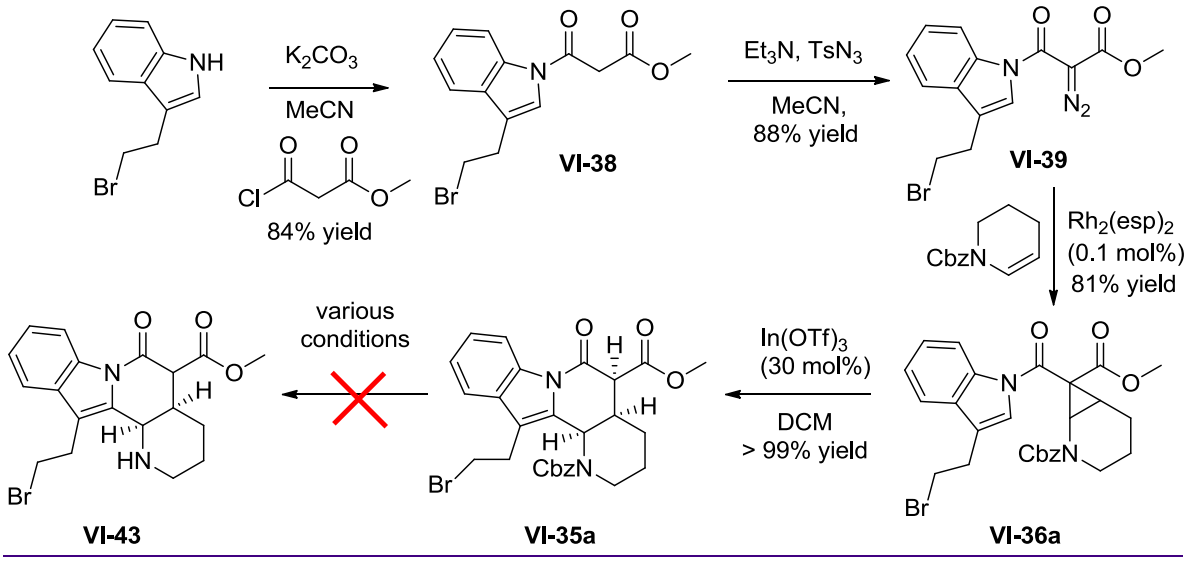


Figure 6.13. First Generation Synthetic Approach for (±)-Deethyleburnamonine

To alleviate this issue, a Boc-protected 2,3-dihydropyridine was employed as the alkene for cyclopropanation, which afforded cyclopropane **VI-37b** in 49% yield (Figure 6.14). The lower yield observed for the Boc-protected enamine is most likely due to the increased steric interference in the transition state between the *t*-Bu group of the enamine and the multi-dentate *esp* ligand of the rhodium carbenoid during cyclopropanation. Cyclization of **VI-37b** similarly provided the all-*cis* diasteromer **VI-36b (**~3:1 *dr*) but with less efficiency than the Cbz case (97% vs 71%), which may also be a result of the steric influence of the Boc *t*-butyl group. Fortunately, when **VI-36b** was subjected to TFA, both deprotection and C-ring closure occurred, generating **VI-35** in 87% yield. Finally, Krapcho decarbalkoxylation[23] provided (±)-deethyleburnamonine **VI-6a** in 85% yield.

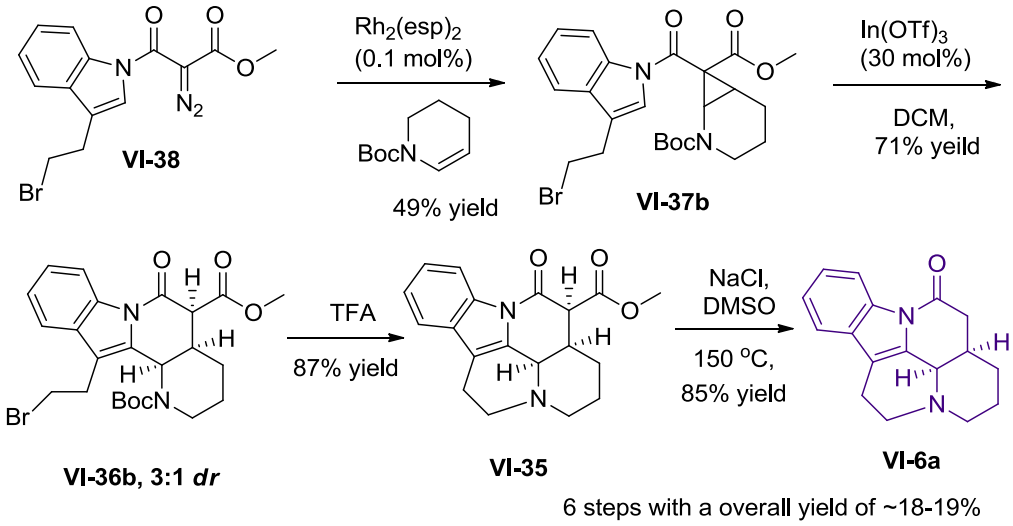


Figure 6.14. Modified Synthetic Approach for (±)-Deethyleburnamonine

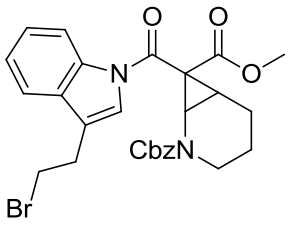
6.4. CONCLUSIONS

In summary, a concise, diastereoselective total synthesis of (±)-deethyleburnamonine is reported. The key steps of the synthesis involve: (a) a tandem ring-opening/Friedel-Crafts alkylation to assemble the tetracyclic ABDE ring system with a *cis* D/E fused ring junction; (b) a TFA-promoted *N*-Boc deprotection/*N*-alkylation to generate the C-ring; and (3) a Krapcho decarbalkoxylation to generate the target. Using this protocol, (±)-deethyleburnamonine was rapidly obtained in ~18-19% overall yield over six steps.

6.5. EXPERIMENTAL

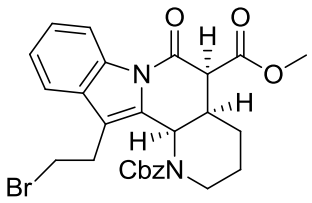
All reactions were carried out in pre-dried glassware from the oven where additional moisture was removed by flame drying the reaction vessel. Each reaction proceeded under a nitrogen atmosphere, and dry solvents were used, unless stated otherwise. Tetrahydrofuran and diethyl ether were distilled from a sodium/benzophenone ketyl under nitrogen and stored in a Schlenk flask. Acetonitrile and dichloromethane were purified by distillation from CaH_2 under N_2 prior to use. All other reagents were purchased from Acros, Sigma-Aldrich, Fluka, VWR, Merck, Alfa Aesar, TCI and Strem (for metal catalysts) and used without further purification. Chromatographic purification was performed as flash chromatography with Dynamic Adsorbents silica gel (32-65 μm) and solvents indicated as eluent with 0.1-0.5 bar pressure. For quantitative flash chromatography, technical grade solvents were utilized. Analytical thin-layer chromatography (TLC) was performed on EMD silica gel 60 F254 TLC glass plates. Visualization was accomplished with UV light, aqueous basic potassium permanganate ($KMnO_4$) solution, iodine, aqueous acidic dinitrophenylhydrazine (DNP) solution, aqueous acidic *p*-anisaldehyde (PAA) solution, and ethanol solution of phosphomolybdic acid (PMA) followed by heating. Each yield refers to isolated analytically pure material. Infrared (IR) spectra were obtained using a Nicolet 4700 FTIR with an ATR attachment from SmartOrbit Thermoelectronic Corp. The IR bands are characterized as weak (w), medium (m), and strong (s). Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Varian Mercury Vx 300 spectrometer or a Varian Mercury Vx 400 spectrometer with solvent resonances as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as

follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, t = triplet, m = multiplet), coupling constants (Hz), and integration. Mass spectra were obtained using a VG-70SE instrument.



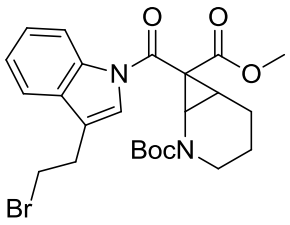
Preparation of *N*-Cbz-protected aminocyclopropane (VI-36a). In a round bottom flask charged with a magnetic stir bar, Rh_2esp_2 (1.4 mg, 1.87 μmol) was dissolved in CH_2Cl_2 (6 mL). The reaction vessel was cooled to 0 ˚C and benzyl 3,4-dihydropyridine-1(2*H*)-carboxylate (0.037 g, 0.187 mmol) was added. After 10 min, 3-(3-(2-bromoethyl)-1*H*-indol-1-yl)-2-diazo-3-oxopropanoate **VI-39** (0.085 g, 0.243 mmol) was dissolved in CH_2Cl_2 (2 mL) and syringed into the reaction mixture. After 10 min, the ice bath was removed and the reaction proceeded at room temperature. After 12 h, the solution was quenched with saturated thiourea and stirred for 30 min. The organic layer was separated and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (30% EtOAc/Hex, R_f 0.25) to afford **VI-36a** as a light brown oil (0.081 g, 81%). (Rotamers!!!) **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.47 (d, *J* = 8.2 Hz, 1H), 7.57 – 7.28 (m, 8H), 7.05 (d, *J* = 43.0 Hz, 1H), 5.19 (d, *J* = 3.2 Hz, 2H), 4.74 (d, *J* = 21.7 Hz, 1H), 3.79 (d, *J* = 3.3 Hz, 3H), 3.71 – 3.51 (m, 4H), 3.35 – 3.10 (m, 3H), 2.46 – 2.25 (m, 1H), 2.25 – 2.01 (m, 1H), 2.00 – 1.76 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.4, 168.3, 167.3, 167.2, 165.7, 165.7, 165.6,

165.5, 153.5, 152.9, 136.0, 135.9, 130.3, 130.1, 130.0, 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 126.8, 126.5, 126.3, 125.9, 125.7, 124.3, 124.1, 123.3, 123.1, 122.9, 122.4, 122.2, 120.4, 119.7, 119.2, 119.1, 118.6, 117.4, 117.1, 116.9, 116.7, 111.4, 111.3, 110.7, 110.6, 67.8, 67.7, 58.0, 57.9, 57.7, 53.4, 52.9, 52.9, 52.8, 43.3, 42.1, 41.9, 38.8, 38.7, 31.3, 30.9, 28.6, 28.4, 23.7, 23.2, 23.0, 22.9, 21.2, 19.3, 19.2. **IR**: 2951.9 (w), 2928.1 (w), 2847.1 (w), 1761.3 (s), 1703.26 (s), 1451.7 (s), 1370.7 (m), 1275.5 (m), 1218.3 (m), 1170.7 (m), 742.1 (s) cm^{-1}. **HRMS** (ESI) M/Z^+ Calc. 538.1103, Obs. 538.1094.



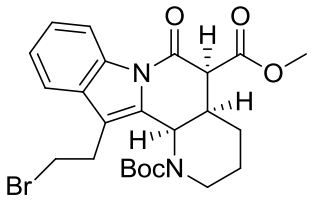
Preparation of *N*-Cbz-protected ABDE tetracycle (VI-35a). 2-Benzyl 7-methyl 7-(3-(2-bromoethyl)-1*H*-indole-1-carbonyl)-2-azabicyclo[4.1.0]heptane-2,7-dicarboxylate **VI-36a** (0.045 g, 0.083 mmol) was added to a solution of $In(OTf)_3$ (0.014 g, 0.025 mmol) in CH_2Cl_2 (3 mL) at room temperature. Upon completion as monitored by TLC, the reaction mixture was quenched with water and extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (25% EtOAc/Hex, R_f 0.25) to afford **VI-35a** as a pale brown oil (0.098 g, 98%) after 2 h. *Diastereomeric ratio: (8:1).* **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.41 (dd, *J* = 14.5, 6.9 Hz, 1.07), 7.50 – 7.19 (m, 9.14), 5.93 (dd, *J* = 17.0, 4.6 Hz, 1), 5.30 – 5.06 (m, 2.54), 4.09 (d, *J* = 13.2 Hz, 1.16), 3.92 – 3.57 (m, 4.64), 3.56 – 2.76 (m, 5.17), 2.75 – 2.48 (m, 2.28), 1.77 (d, *J* = 10.4 Hz, 1.25), 1.53 (s, 2.17), 1.43 – 1.26 (m, 1.08). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.1, 162.8, 155.1, 136.0, 134.7, 130.2, 130.0, 129.1, 129.0, 128.5, 128.2,

128.1, 125.6, 125.5, 124.4, 124.3, 117.9, 117.8, 117.0, 116.7, 116.5, 68.2, 68.1, 55.9, 53.1, 52.5, 48.3, 42.5, 39.7, 37.7, 30.0, 27.2, 27.5, 26.6, 24.6. **IR**: 2950.4 (w), 2910.7 (w), 2880.6 (w), 1755.7 (s), 1719.2 (s), 1442.8 (m), 1275.6 (m), 758.2 (s) cm^{-1}. **HRMS** (ESI) M/Z^+ Calc. 538.1103, Obs. 538.1105.



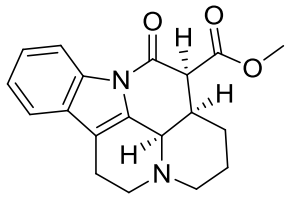
Preparation of *N*-Boc-protected aminocyclopropane (VI-37b). In a round bottom flask charged with a magnetic stir bar, Rh_2esp_2 (1.0 mg, 1.319 μmol) was dissolved in CH_2Cl_2 (15 mL). The reaction vessel was cooled to 0 ˚C and tert-butyl 3,4-dihydropyridine-1(2*H*)-carboxylate (0.201 g, 1.098 mmol) was added. After 10 min, methyl 3-(3-(2-bromoethyl)-1*H*-indol-1-yl)-2-diazo-3-oxopropanoate **VI-38** (0.500 g, 1.422 mmol) was dissolved in CH_2Cl_2 (5 mL) and syringed into the reaction mixture. After 10 min, the ice bath was removed and the reaction proceeded at room temperature. After 12 h, the solution was quenched with saturated aqueous thiourea and stirred for 30 min. The organic layer was separated and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (30% EtOAc/Hex, R_f 0.25) afforded **VI-37b** as a colorless oil (0.271 g, 49%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.47 (d, *J* = 8.1 Hz, 1H), 7.56 – 7.45 (m, 1H), 7.43 – 7.28 (m, 2H), 6.98 (d, *J* = 66.6 Hz, 1H), 4.74 (d, *J* = 9.4 Hz, 1H), 3.79 (d, *J* = 3.8 Hz, 3H), 3.70 – 3.35 (m, 4H), 3.27 (t, *J* = 6.9 Hz, 2H), 3.17 (t, *J* = 6.8 Hz, 1H), 2.45 – 2.04 (m, 2H), 1.93 – 1.76 (m, 2H), 1.47 (d, *J* = 7.5 Hz, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ

168.6, 165.8, 152.6, 151.8, 136.1, 129.9, 129.8, 127.9, 126.9, 126.7, 125.8, 124.1, 122.2, 121.9, 120.3, 119.6, 118.4, 117.1, 110.1, 109.3, 81.2, 81.1, 58.2, 52.9, 43.3, 42.2, 41.1, 34.6, 31.6, 31.2, 28.5, 28.4, 28.2, 25.3, 23.7, 23.0, 22.6, 21.4, 14.1. **IR**: 2998 (w), 2942.3 (w), 1725.2 (s), 1628.9 (s), 1468.9 (s), 1342.1 (s), 1185.6 (s), 760.4 (s) cm^{-1}. **HRMS** (ESI) M/Z^+ Calc. 504.1300, Obs. 504.1251.

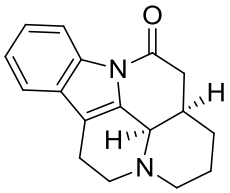


Preparation of *N*-Boc-protected ABDE tetracycle (VI-36b). 2-*tert*-Butyl 7-methyl 7-(3-(2-bromoethyl)-1*H*-indole-1-carbonyl)-2-azabicyclo[4.1.0]heptane-2,7-dicarboxylate **VI-37b** (0.075 g, 0.148 mmol) was added to a solution of $In(OTf)_3$ (0.030 g, 0.053 mmol) in CH_2Cl_2 (10 mL) at room temperature. Upon completion as determined by TLC, the reaction mixture was quenched with water and extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (25% EtOAc/Hex, R_f 0.30) to afford **VI-36b** as a colorless oil (0.053 g, 71%) after 3 h. *Diastereomeric ratio: (3.2:1).* **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.55 – 8.43 (m, 1.11H), 7.57 – 7.49 (m, 1.16), 7.42 – 7.30 (m, 2.5), 5.97 (s, 1), 4.05 (t, *J* = 11.6 Hz, 090), 3.84 (s, 1), 3.76 (d, *J* = 3.9 Hz, 2.87), 3.73 – 3.63 (m, 1.17), 3.52 (dt, *J* = 20.5, 12.0 Hz, 2.33), 3.33 – 3.05 (m, 2.64), 2.65 (d, *J* = 12.1 Hz, 2.39), 2.29 (d, *J* = 10.6 Hz, 0.22), 1.86 (d, *J* = 13.0 Hz, 1), 1.69 – 1.49 (m, 13.63). **^{13}C NMR** (75 MHz, $CDCl_3$) 168.2, 167.5, 163.0, 154.6, 154.3, 134.7, 134.5, 130.3, 130.1, 130.0, 129.7, 129.5, 125.4, 124.4, 124.2, 118.0, 117.9, 117.8, 116.7, 116.5, 81.1, 81.1, 56.0, 53.6, 53.1, 52.5, 50.2, 42.5,

40.3, 39.9, 37.6, 29.9, 28.4, 28.3, 27.5, 26.8, 24.7, 24.4, 22.8. **IR**: 2997.9 (w), 2961.3 (w), 1766.3 (m), 1726.7 (s), 1469.1 (s), 1186.1 (m), 760.3 (s), 663.1 (m) cm^{-1}. **HRMS** (ESI) M/Z^+ Calc. 504.1300, Obs. 504.1255.



Preparation of *N*-Boc-protected pentacycle (VI-35). Tetracycle **VI-36b** (0.030 g, 0.059 mmol) was dissolved in trifluoroacetic acid (2 mL) and stirred for 2 h. Saturated aqueous $NaHCO_3$ was slowly added to quench the reaction. The resulting mixture was extracted three times with CH_2Cl_2, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (1.5% $MeOH/CH_2Cl_2$, R_f 0.40) to afford **VI-35** as a colorless oil (0.0168 g, 87% yield). *Diastereomeric ratio: (5:1).* **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.41 – 8.30 (m, 1.11), 7.46 – 7.40 (m, 1.27), 7.36 – 7.25 (m, 2.45), 4.46 – 4.34 (m, 1.11), 3.84 (s, 0.60), 3.75 (d, *J* = 3.8 Hz, 3.24), 3.68 – 3.59 (m, 9.42), 3.36 – 3.28 (m, 2.61), 2.98 – 2.74 (m, 3.24), 2.68 – 2.33 (m, 4.88), 1.65 (ddd, *J* = 10.6, 9.2, 7.6 Hz, 4.01). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.6, 167.4, 164.0, 160.9, 135.3, 135.0, 128.4, 128.3, 127.7, 127.5, 126.9, 126.4, 124.8, 124.0, 122.1, 120.9, 120.3, 118.8, 117.2, 116.7, 112.6, 104.9, 77.4, 77.0, 76.6, 70.3, 55.3, 53.6, 53.1, 49.5, 48.4, 44.2, 35.8, 33.8, 32.4, 29.6, 27.0, 24.8, 16.1, 14.6. **HRMS** (ESI) M/Z^+ Calc. 324.1434, Obs. 324.1470.



Preparation of (±)-Deethyleburnamonine (VI-6a). To a 10 mL round bottom flask equipped with a stir bar, β-amide ester **VI-35** (0.050 g, 0.154 mmol), NaCl (9.46 mg, 0.161 mmol), water (5.55 μL, 0.308 mmol) and DMSO (3 mL) were added at room temperature. The flask was fitted with a reflux condenser and heated to 150 ˚C with vigorous stirring. After heating for 16 h, TLC analysis indicated consumption of starting material. The reaction was cooled and diluted with 7:3 Hexanes/Et_2O (25 mL) and washed three times with water. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (1.5% MeOH/CH_2Cl_2, R_f 0.40) to afford **VI-6a** as a white solid (0.0349 g, 85% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.46 – 7.41 (m, 1H), 7.36 – 7.27 (m, 2H), 4.40 – 4.30 (m, 1H), 3.39 – 3.29 (m, 2H), 3.02 – 2.83 (m, 2H), 2.72 – 2.57 (m, 3H), 2.46 (qdd, *J* = 10.9, 5.3, 3.1 Hz, 3H), 1.69 – 1.55 (m, 3H), 1.00 – 0.81 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.3, 134.3, 131.3, 129.8, 124.3, 123.8, 118.0, 116.2, 112.7, 53.4, 50.4, 44.5, 39.7, 34.3, 25.3, 24.7, 16.3. The physical characterization of the product matches the previously reported data in the literature (see ref. 22).[18, 24]

6.6. REFERENCES

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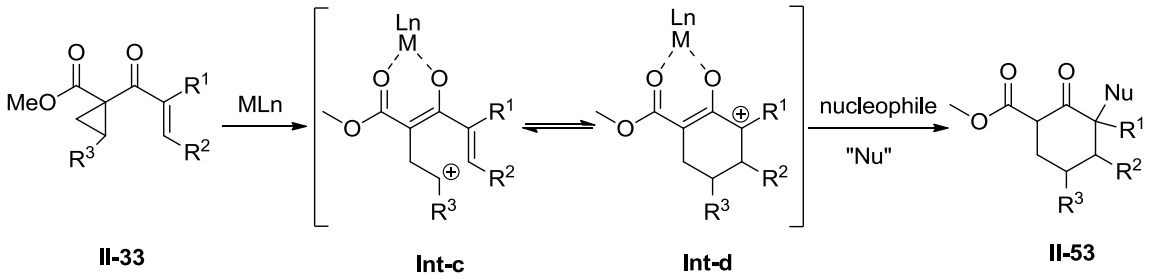
APPENDIX A

FUTURE WORK

The results obtained from the projects in this thesis have often been unexpected and interesting, and thus prompt further investigation that was not able to be completed during the time frame of theses project.

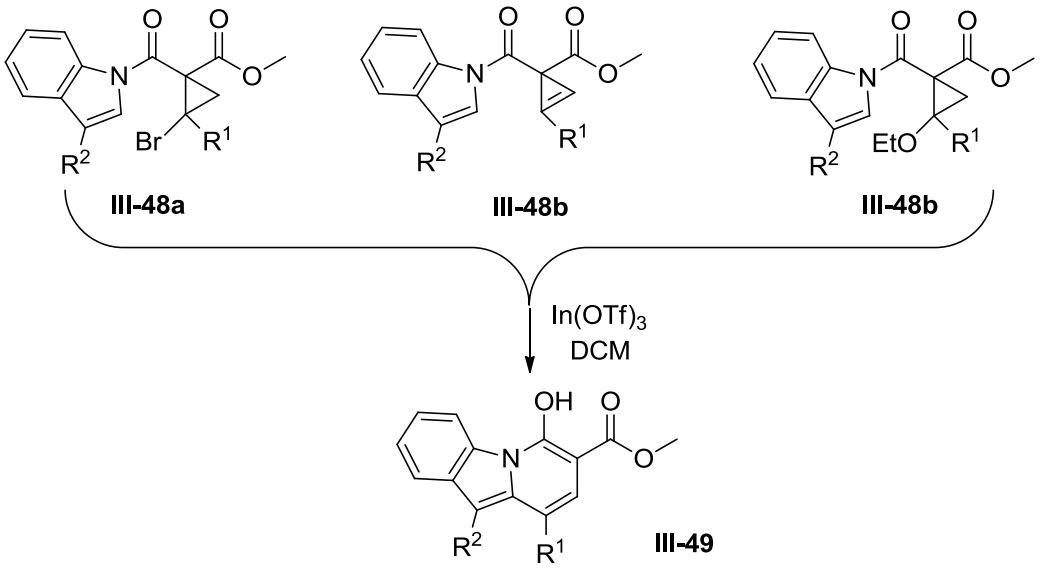
1. Interrupted Homo-Nazarov Cyclization: A Trapping of the Oxy-Allyl Cationic Intermediate with a Suitable Nucleophile

As detailed in Chapter 2, alkenyl cyclopropyl ketones such as **II-33** undergo a homo-Nazarov cyclization reaction in the presence of catalytic amounts of $In(OTf)_3$ to furnish cyclohexenone and methylene cyclohexenol derivatives. This reaction proceeds via an oxyallyl cationic intermediate **Int-d**. Although mechanistically distinct, this reaction is homologous to the Nazarov cyclization, as it proceeds via a similar cyclic oxyallyl cationic intermediate. While the interrupted Nazarov cyclization reaction has been studied in great detail, much less is known about the homologous homo-Nazarov cyclization reaction. The interruption with a suitable nucleophile such as amines, alcohols, or allyl silanes could lead to a wide range of new and interesting α-substituted cyclohexenone derivatives **II-53**. This project is currently underway within the research group.



2. Novel Pyrido[1,2-*a*]indole-based Fluorescent Probes with Varying Emission Colors for Imaging in Living Cells

While the majority of the research described in Chapter 3 showed that hydropyrido[1,2-*a*]indole-6(7*H*)-ones derivatives were efficiently obtained using our tandem cyclopropane ring-opening/Friedel-Crafts reaction sequence, additional work to generate pyrido[1,2-*a*]indole-based fluorescent compounds with varying emission colors for imaging living cells would be of interest. Some initial reactions mentioned within this thesis had limited success, yet these analogues might be accessible in high yields through optimization of the reaction conditions. Alternative reaction pathways based on the use of In(III)-catalyzed cycloisomerization of either *N*-indolyl cyclopropen-3,3-dicarbonyl compounds or *N*-indolyl cyclopropanes substituted with acylic ethers could be highly useful. Additional studies direct towards this end are currently underway in our laboratory.

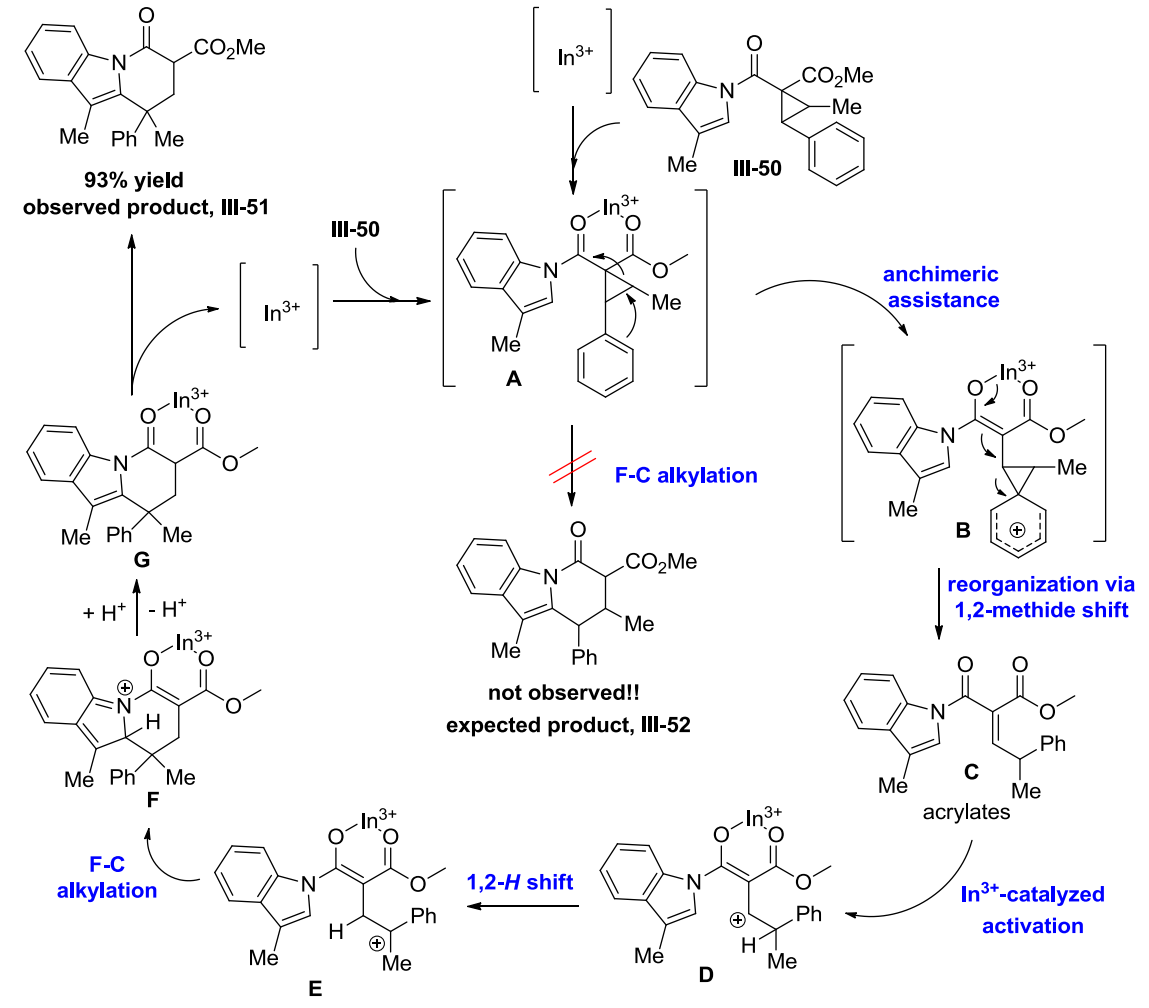


3. Experimental and Theoretical Studies on the In(III)-Catalyzed Rearrangement and Cyclization of *N*-Indolyl Cyclopropanes and *N*-Indolyl Alkylidene Malonate Monoamides

As was reported in Chapter 3, *N*-indolyl cyclopropanes undergo a tandem cyclopropane ring-opening/Friedel-Crafts alkylation reaction in the presence of 30 mol% of $In(OTf)_3$. However, vicinally disubstituted cyclopropane **III-50** (derived β-methyl styrene) afforded hydropyrido[1,2-*a*]indole product **III-51**, none of the anticipated product **III-52** was observed. The formation of this product could be explained if the cyclopropane undergoes a ring-opening via anchimeric assistance from phenyl donor group **A** to form phenonium intermediate species **B**, which subsequently reorganizes via 1,2-methide shift to generate *N*-indolyl alkylidene malonate monoamide precursor **C**. An In(III)-catalyzed activation of monoamide then gives rise to carbocationic intermediate **D** which then undergoes a further 1,2-hydride shift to form carbocation **E.** An intramolecular Friedel-Crafts reaction generates the observed product **III-51**. Further

mechanistic examination of this cationic rearrangement pathway is currently underway in the France lab.

Along these lines, a detailed mechanistic investigation into the divergent reaction pathway of a cationic intermediate **B** generated when monoamide **IV-35r** (derived from isobutyraldehyde) was subjected to cyclization conditions would be of significant interest (Figure 4.12, Chapter 4).



VITA

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The author was born in Madaj (Osmanabad, MH), India on the 2nd of May, 1983. In 2000, he enrolled at the **I**nstitute of **C**hemical **T**echnology (ICT, erstwhile **U**niversity **D**epartment of **C**hemical **T**echnology, UDCT). While at ICT his studies majored in the Technology of Intermediates and Dyestuffs. As a part of an undergraduate research project, he pursued the synthesis of "Iron Complexed Formazan Dyes from 1,5-Diphenyl-3-cyano," under the direction of Prof. V. R. Kanetkar and Professor N. Sekar. In 2004, he graduated with a Bachelors of Chemical Technology (B.Tech.).

Upon completion of his undergraduate studies he joined Gharda Chemicals Limited (GCL), Dombivli (India). During his three years of work in high performance pigments division at GCL, he worked on the design and development of organic pigments for their application in high performance coatings/paints, inks and plastics under the tutelage of Dr. A.B. Karnik and Dr. A.B. Shah.

In the fall of 2007 he embarked on his graduate studies in the field of synthetic methodology development and natural product synthesis in the laboratory of Prof. Stefan France at the Georgia Institute of Technology (GeorgiaTech). He defended this thesis in July 2012.